Comparative Effectiveness Review

Number 63

First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10021

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Errata – On August 20, 2012, Appendix O was updated to clarify that the route of administration for INVEGA SUSTENNA is IM injection (dosage 39 mg - 234 mg) and the route of administration for RISPERIDOL CONSTA is IM injection (dosage 25 mg).

AHRQ Publication No. 12-EHC054-EF
August 2012

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Abou-Setta AM, Mousavi SS, Spooner C, Schouten JR, Pasichnyk D, Armijo-Olivo S, Beaith A, Seida JC, Dursun S, Newton AS, Hartling L. First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness. Comparative Effectiveness Review No. 63. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021.) AHRQ Publication No. 12-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to Beth Collins Sharp at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Ms. Annabritt Chisholm (article retrieval), Ms. Teodora Radisic (article retrieval), Mr. Ben Vandermeer (data analysis), and Ms. Andrea Milne (literature searching). We acknowledge Ms. Christine Ha, Ms. Elizabeth Sumamo Schellenberg, and Mr. Kai Wong for help in screening the gray literature.

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First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

Structured Abstract

Objectives. To compare individual first-generation antipsychotics (FGAs) with individual second-generation antipsychotics (SGAs) in adults (18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, with a focus on core illness symptoms, functional outcomes, health care system utilization, and adverse events.

Data Sources. We conducted comprehensive searches in 10 electronic databases up to July 2011. We hand-searched conference proceedings, clinical trials registers, and reference lists of relevant studies. We contacted content experts and authors of relevant studies.

Methods. Two reviewers independently conducted study selection, assessed methodological quality, extracted data, and graded the strength of evidence. We conducted a descriptive analysis and performed meta-analyses when appropriate.

Results. We included 113 studies of schizophrenia (22 comparisons) and 11 studies of bipolar disorder (6 comparisons), and 1 study included both. Trials (n = 123) had an unclear (63 percent) or high (37 percent) risk of bias. Cohort studies (n = 2) had good methodological quality.
Core illness symptoms (global ratings and total scores). For schizophrenia, clozapine was more efficacious than chlorpromazine based on the one reported scale. Results for haloperidol versus olanzapine were discordant, with olanzapine favored for one scale but no differences based on two other scales. Haloperidol was favored over quetiapine based on one of four scales reported. No differences were found for haloperidol versus aripiprazole, clozapine, risperidone, and ziprasidone.
For bipolar disorder, haloperidol was favored over ziprasidone on the one scale reported. No differences were observed for haloperidol versus aripiprazole, olanzapine, or risperidone.
Functional outcomes and health care system utilization. Evidence came primarily from single studies and showed no differences between groups.
Adverse events. No differences were found in mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole, or in metabolic syndrome for haloperidol versus olanzapine. The most frequently reported adverse events with significant differences were extrapyramidal symptoms; in most cases, the SGA had fewer extrapyramidal symptoms than haloperidol.
Other outcomes. For schizophrenia, few differences were found across comparisons and outcomes. No differences were observed in health-related quality of life. For bipolar disorder, there were few comparisons or differences.
Subgroups. The most common subgroups were race and treatment resistance. No notable differences were found compared with overall results.

Conclusion. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the four key adverse events deemed a priori to be most clinically important.

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Executive Summary

Introduction

Antipsychotic medications are used to treat and manage symptoms for several psychiatric disorders and are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as "typical antipsychotics," were developed in the 1950s. Second-generation antipsychotics (SGAs), also known as "atypical antipsychotics," emerged in the 1980s. To date, FGAs have been classified according to their chemical structure, which includes serotonin-dopamine antagonists and multiacting receptor-targeted antipsychotics, whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists. There is ongoing research testing the proposed mechanisms of action within each class with respect to the neurobiology of different psychiatric disorders.[1,2]

According to findings from the 2004–05 Medical Expenditure Panel Survey, an estimated 2 million adult patients in the United States were prescribed an antipsychotic medication, three-quarters of whom were taking an SGA.[3] In 2003, an estimated $2.82 billion were spent in the country on these medications, with SGAs accounting for 93 percent of this expenditure.[3] Today, 20 FGAs and SGAs are commercially available in the United States and approved by the Food and Drug Administration (FDA).

Individuals taking antipsychotics may stop taking their medication for a number of reasons, including adverse events (AEs) and a lack of improvement in their symptoms.[4] As a result, ongoing evaluations of drug efficacy and models of patient decisionmaking are essential.

This Comparative Effectiveness Review (CER) provides a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs. In contrast to previous reviews, this CER focuses on comparisons of individual medications rather than drug classes. This topic is important and timely, given the ongoing debate about the comparative benefits and harms of FGAs and SGAs.[5] Moreover, the focus of this report complements other recent reviews investigating different SGAs,[6] the off-label use of antipsychotics,[7] and FGAs versus SGAs in the pediatric population.[8] The focus of this report is adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. This age group is the normal demographic in which these illnesses have been shown to be prevalent. The illnesses are discussed in more detail in the sections that follow.

Key Questions

The following Key Questions (KQs) were investigated in the report:

1. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms? The following core symptoms were considered:
    a. Schizophrenia or related psychoses: positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms, general psychopathology (i.e., preoccupation, lack of insight, and motor retardation), and global ratings and total scores.
    b. Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

2. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?
    a. Functional outcomes include any of the following: employment or personal earnings, social relatedness or functioning, encounters with the legal system, sexual function or dysfunction, functional capacity, and living situation.
    b. Health care system utilization includes: time to hospitalization or rehospitalization because of mental illness and all other causes, rates of hospitalization or rehospitalization, mean hospital bed days, length of hospitalization stay, rates of emergency department visits, attendance in day care programs, and use of ancillary caseworkers.
3. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety? AEs included:
    a. Overall AEs.
    b. Specific AEs:
        i. *Major:* mortality, cerebrovascular disease–related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide.
        ii. *General:* extrapyramidal symptoms (EPS), weight changes, agitation, constipation, sedation, elevated cholesterol, AEs related to prolactin elevations, galactorrhea or bloody galactorrhea, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).
    c. Study withdrawals and time to withdrawal because of AEs.
    d. Persistence and reversibility of AEs.
4. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes:
    a. Relapse and remission rates.
    b. Medication adherence and persistent use (and associated dosing and time to discontinuation of treatment).
    c. Patient insight into illness.
    d. Health-related quality of life.
    e. Patient satisfaction.
    f. Comorbidity: endpoints of victimization, homelessness, and substance abuse.
    g. Patient-reported outcomes.
    h. Ability to obtain and retain employment and succeed in job duties.
    i. Concomitant use of other medications, especially those used to treat EPS.
    j. Patient preferences.

5. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?
    a. Disorder subtypes.
    b. Sex.
    c. Age group (18–35 years, 36–54 years, and 55–64 years).
    d. Race.
    e. Comorbidities.
    f. Drug dosage.
    g. Followup period.
    h. Treatment of a first episode versus treatment in the context of previous episodes (previous exposure to antipsychotics).
    i. Treatment resistance.

Methods

In general, we followed methodologically rigorous methods for systematic reviews as described in recent standards documents.[7,8] Detailed information on the reports prepared by Evidence-based Practice Centers can be found on the Agency for Healthcare Research and Quality Web site at www.effectivehealthcare.ahrq.gov/.

Literature Search

We conducted comprehensive searches in the following electronic databases: MEDLINE®, Embase, PsycINFO, International Pharmaceutical Abstracts, CINAHL, ProQuest® Dissertations and Theses–Full Text, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus™. The searches are up to date to July 2011. For the questions on AEs, we also searched the U.S. National Library of Medicine's TOXLINE® and the MedEffect™ Canada Adverse Drug Reaction Database.

We hand-searched proceedings for the Annual Convention of the American Psychiatric Association (2008–10), the International College of Neuropsychopharmacology (2008–10), and the International Society for Bipolar Disorders (2008–10). We searched clinical trials registers, contacted experts in the field, and contacted authors of relevant studies. In addition, we reviewed the reference lists of reviews and guidelines and searched for articles citing the studies that met our inclusion criteria using Scopus™ Citation Tracker.

Study Selection

Two reviewers independently screened titles and abstracts to determine if an article met the broad inclusion criteria for study design, population, interventions, and comparators. We independently rated each article as "include," "exclude," or "unclear." We retrieved the full text of studies identified as "include" or "unclear." Two reviewers independently reviewed each article using a priori eligibility criteria and a standardized form. We resolved discrepancies through discussion and consensus or by third-party adjudication.

We included studies if they: were randomized (RCTs) or nonrandomized controlled trials (nRCTs), or prospective or retrospective cohort studies with a followup of 2 years or greater; included adults age 18 to 64 years with schizophrenia or related psychoses or bipolar disorder; and compared a commercially available FDA-approved FGA with an FDA-approved SGA.

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies and resolved disagreements through discussion and consensus or third-party adjudication. We assessed RCTs and nRCTs using the Cochrane Collaboration's Risk of Bias tool.[5] We assessed cohort studies using the Newcastle-Ottawa Scale.[7] A priori, the research team developed decision rules regarding application of the tools.

Two reviewers independently evaluated the overall strength of evidence (SoE) using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach used by Evidence-based Practice Centers and resolved discrepancies through discussion. We examined the following four major domains: risk of bias (low, medium, or high), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct or indirect), and precision (precise or imprecise). We assigned an overall evidence grade of "high," "moderate," "low," or "insufficient."

We graded core illness symptoms in the categories of positive symptoms, negative symptoms, general psychopathology, and global ratings and total scores. We provided a grade for each different scale that was used. We graded the following AEs, which were deemed to be most clinically important a priori: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. These outcomes were identified a priori as being the most clinically important for decisionmaking.

Data Extraction

Two reviewers independently extracted data using standardized data extraction forms and resolved discrepancies through discussion and consensus or by third-party adjudication. We extracted information on study characteristics, population, interventions and dosing regimens, outcomes assessed, results, and funding source. When studies incorporated multiple relevant treatment arms or multiple followup periods, we extracted data from all groups for the longest followup data. When there were multiple reports of the same study, we referenced the primary or most relevant study and extracted only additional data from companion reports.

Data Analysis

We presented evidence tables for all studies and a qualitative description of results. We conducted meta-analyses using random effects models to answer the KQs when studies were sufficiently similar in terms of design, population, interventions, and outcomes. We presented results separately for the conditions of interest (schizophrenia or schizophrenia-related psychoses and bipolar disorder). Within each condition, we presented results separately for each individual comparison of FGA versus SGA. We quantified statistical heterogeneity using the I-squared (I^2) statistic.

Applicability

We assessed the applicability of the body of evidence using the PICOTS format (population, intervention, comparator, outcomes, timing of outcome measurement, and setting). We reported factors that may potentially limit the applicability of the results. These included patient characteristics (e.g., age, diagnostic criteria, severity of illness, comorbidities, concomitant medications, inpatient or outpatient status) and study characteristics (e.g., length of followup).

Results

Description of Included Studies

The searches identified 9,411 unique study reports. A total of 125 primary publications and 146 companion publications were included. The studies included 121 RCTs, 2 nRCTs, and 2 retrospective cohort studies. The studies were published between 1974 and 2010. The majority of studies were multicenter (n = 70, 56 percent) and involved inpatients (n = 62, 50 percent), and they were conducted more often in North America than elsewhere (n = 57, 46 percent). The number of participants in the studies ranged from 10 to 95,632 (median = 86 [interquartile range (IQR), 36 to 300]). The average age of study participants ranged from 21 to 50 years (median = 37 years [IQR, 33 to 41]). The length of followup ranged from <1 day to 22 years (median = 8 weeks [IQR, 6 to 26 weeks]). Seventy percent of studies (n = 88) had some form of support from the pharmaceutical industry.

Overall, 113 studies examined schizophrenia or schizophrenia-related psychoses, 11 studies examined bipolar disorder, and 1 study included both. A total of 22 and 6 drug comparisons were made for schizophrenia and bipolar disorder, respectively (Table A).

Table A. Comparisons examined in the included studies

Schizophrenia or Schizophrenia-Related Psychoses		Bipolar Disorder	
Comparison	***n***	***Comparison***	***n***
Chlorpromazine vs. clozapine	12	Chlorpromazine vs. clozapine	1
Chlorpromazine vs. olanzapine	1	Haloperidol vs. aripiprazole	2
Chlorpromazine vs. quetiapine	1	Haloperidol vs. olanzapine	2
Chlorpromazine vs. ziprasidone	1	Haloperidol vs. quetiapine	1
Fluphenazine vs. olanzapine	2	Haloperidol vs. risperidone	5
Fluphenazine vs. quetiapine	1	Haloperidol vs. ziprasidone	1
Fluphenazine vs. risperidone	1		
Haloperidol vs. aripiprazole	8		
Haloperidol vs. asenapine	1		
Haloperidol vs. clozapine	11[a]		
Haloperidol vs. olanzapine	35[a]		
Haloperidol vs. quetiapine	11[a]		
Haloperidol vs. risperidone	39[b]		
Haloperidol vs. ziprasidone	9[c]		
Perphenazine vs. aripiprazole	1		
Perphenazine vs. olanzapine	2		
Perphenazine vs. quetiapine	1		
Perphenazine vs. risperidone	2		
Perphenazine vs. ziprasidone	1		
Trifluoperazine vs. clozapine	1		
Thioridazine versus clozapine	1		
Thioridazine versus risperidone	1		

n = number of studies; nRCT = nonrandomized controlled trial

Note: n = 125.

[a]Includes 1 cohort study.

[b]Includes 1 cohort study and 1 nRCT.

[c]Includes 1 nRCT.

Methodological Quality of Included Studies

None of the 123 RCTs and nRCTs was rated as having a low risk of bias. The majority of the trials (n = 78, 63 percent) had an unclear risk of bias; the remaining trials (n = 45, 37 percent)

had a high risk of bias. In the majority of cases, trials were assessed as having unclear risk of bias due to unclear reporting with respect to sequence generation, concealment of allocation, and methods of blinding. The most common reasons for trials to be assessed as having high risk of bias were lack of blinding and inadequate handling or reporting of outcome data.

Data were collected retrospectively in both cohort studies. The methodological quality of the cohort studies was good.

Results of Included Studies

The results are presented by the KQs they address. Within each KQ, we present results by condition and comparison. Tables with a summary of findings for efficacy and safety are presented below. It is important to note that lack of statistical significance does not equate to equivalence or noninferiority, nor does statistical significance equate to clinical significance.

KQ1: Core Illness Symptoms

The findings for core illness symptoms are presented for each condition in Table B. Comparisons and outcomes for which there was insufficient SoE to draw a conclusion (e.g., evidence from single trials) are not displayed in the tables. The SoE comparing individual FGAs and SGAs was insufficient to draw conclusions for the following comparisons: chlorpromazine versus olanzapine, quetiapine, and ziprasidone; fluphenazine versus olanzapine, quetiapine, and risperidone; haloperidol versus asenapine; perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; trifluoperazine versus clozapine.

For schizophrenia or related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive or negative symptoms or general psychopathology. Clozapine showed benefits for total score (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive symptoms or general psychopathology, global ratings, or total symptom score. The SoE was low for positive outcomes, global ratings, and total scores; the SoE was insufficient for general psychopathology. Aripiprazole showed benefits for negative symptoms (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general psychopathology (low SoE). The findings were discordant for total symptom score: no difference was found based on the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) (low SoE); one study showed benefits for clozapine on the Clinical Global Impression–Improvement (CGI–I) and Clinical Global Impression–Severity (CGI–S) scales (insufficient SoE).

Twenty-seven studies provided data on core illness symptoms for haloperidol versus olanzapine. No differences were found for positive symptoms (low SoE). Olanzapine was favored for negative symptoms (moderate SoE). In terms of general psychopathology, a significant benefit for olanzapine was found based on the Hamilton Rating Scale for Depression (HAM–D), Montgomery-Asberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS). No differences were observed for the other five scales of general symptoms assessed. The SoE varied across outcomes from insufficient to moderate. Olanzapine was favored for global ratings and total symptom scores based on the CGI–S and PANSS; however,

no differences were found for the other four scales assessed. The SoE for these outcomes also varied from insufficient to moderate.

Nine studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive or negative symptoms, or general psychopathology. A significant difference favoring haloperidol was found for one of the five global ratings (CGI–S) and total symptom scores assessed. The SoE across outcomes ranged from insufficient to moderate.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. There were no differences for positive symptoms (low SoE). Risperidone was favored for negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS) (moderate SoE); in contrast, no difference for negative symptoms was found based on PANSS (low SoE). No differences were found for any of the six measures used to assess general psychopathology (low to insufficient SoE). Seven of the global ratings or total symptom scores showed no differences, whereas the Symptom Checklist (SCL–90–R) showed a benefit for risperidone (low to insufficient SoE).

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms, general psychopathology, global ratings, or total score (low to insufficient SoE). No studies provided data on positive symptoms.

A total of 12 studies included patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (five RCTs). No significant differences were found for mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low to insufficient SoE). Two studies compared haloperidol versus olanzapine and found no significant differences in sleep, mood (mania), mood (depression), or global ratings and total scores (low or insufficient SoE). Two studies compared haloperidol with aripiprazole and found no differences in mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low or insufficient SoE). Single studies compared chlorpromazine versus clozapine and haloperidol versus quetiapine and ziprasidone (insufficient SoE).

Table B. Summary of the strength of evidence for core illness symptoms (KQ1)

Outcome	Comparison	SoE	Summary (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses			
Positive symptoms	Haloperidol vs. aripiprazole	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No difference for PANSS (14 RCTs) or SAPS (2 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No difference for PANSS (20 RCTs) or SAPS (2 RCTs).

Table B. Summary of the strength of evidence for core illness symptoms (KQ1) (continued)

Outcome	Comparison	SoE	Summary (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses (continued)			
Negative symptoms	Haloperidol vs. aripiprazole	Moderate	Significant difference favoring aripiprazole for PANSS (3 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs) or SANS (2 RCTs).
	Haloperidol vs. olanzapine	Moderate	Significant difference favoring olanzapine for PANSS (14 RCTs) and SANS (5 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low to moderate	Significant difference favoring risperidone for SANS (moderate SoE, 4 RCTs). No significant difference for PANSS (low SoE, 20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for PANSS (2 RCTs).
General psychopathology	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for HAM–D (moderate SoE, 3 RCTs) and MADRS (moderate SoE, 6 RCTs). No difference for ABS (low SoE, 2 RCTs), ACES (low SoE, 2 RCTs), CDS–S (low SoE, 3 RCTs), HAM–A (low SoE, 2 RCTs), or PANSS (low SoE, 10 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for CDS–S (2 RCTs) or PANSS (4 RCTs).
Global ratings and total scores	Chlorpromazine vs. clozapine	Moderate	Significant difference favoring clozapine for BPRS (6 RCTs).
	Haloperidol vs. aripiprazole	Low	No significant difference for BPRS (3 RCTs) or CGI–S (5 RCTs).
	Haloperidol vs. clozapine	Low	No difference for BPRS (4 RCTs) or PANSS (3 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for CGI–S (moderate SoE, 7 RCTs) and PANSS (moderate SoE, 14 RCTs). No difference for BPRS (low SoE, 13 RCTs) or CGI–I (low SoE, 2 RCTs).
	Haloperidol vs. quetiapine	Low to moderate	Significant difference favoring haloperidol for CGI–S (moderate SoE, 4 RCTs). No difference for BPRS (low SoE, 4 RCTs), CGI–I (low SoE, 3 RCTs), or PANSS (low SoE, 6 RCTs).
	Haloperidol vs. risperidone	Low	No difference for BPRS (13 RCTs), CGI–I (3 RCTs), CGI–S (8 RCTs), or PANSS (20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for BPRS (4 RCTs), CGI–S (4 RCTs), GAF (3 RCTs), or PANSS (4 RCTs).

Table B. Summary of the strength of evidence for core illness symptoms (KQ1) (continued)

Outcome	Comparison	SoE	Summary (Number of Studies)
Bipolar Disorder			
Mood (mania)	Haloperidol vs. aripiprazole	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. risperidone	Low	No significant difference in YMRS (3 RCTs).
Mood (depression)	Haloperidol vs. aripiprazole	Low	No significant difference in MADRS (2 RCTs).
Global ratings and total scores	Haloperidol vs. aripiprazole	Low	No significant difference in CGI–BP (2 RCTs).

ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–BP = Clinical Global Impression–Bipolar; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = strength of evidence; YMRS = Young Mania Rating Scale

KQ2: Functional Outcomes and Health Care System Utilization

The findings for functional outcomes and health care system utilization are presented for each condition and comparison in Table C. We did not assess the SoE for outcomes in KQ2.

Results for functional outcomes were available from nine head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. No significant differences in functional outcomes were observed between groups for any of the comparisons. However, in most cases evidence came from single studies. Results for health care system utilization were available for 10 head-to-head comparisons, and no differences were found for any comparison.

Only one trial comparing haloperidol with olanzapine provided data on functional outcomes in patients with bipolar disorder. Significant differences were found favoring olanzapine in terms of the number of individuals actively working for pay. No differences were found for impairment in household or work activities.

Table C. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2)

Outcome	Comparison	Summary (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses		
Functional outcomes	Fluphenazine vs. quetiapine	No significant difference for sexual dysfunction or improvement on treatment (1 RCT).
	Fluphenazine vs. risperidone	No significant difference for sexual dysfunction or improvement on treatment (1 RCT).
	Haloperidol vs. olanzapine	No significant difference for positive urine toxicology (1 RCT) or sexual dysfunction (1 RCT).
	Haloperidol vs. quetiapine	No significant difference for sexual dysfunction (1 RCT).
	Haloperidol vs. risperidone	No significant difference for economic independence (1 RCT) or attitude regarding drugs (1 RCT).
	Haloperidol vs. ziprasidone	No difference for sexual dysfunction (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. risperidone	No significant difference in patients with paid employment (1 RCT).

Table C. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2) (continued)

Outcome	Comparison	Summary (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses		
Functional outcomes (continued)	Perphenazine vs. ziprasidone	No significant difference in patients with paid employment (1 RCT).
Health care system use	Chlorpromazine vs. clozapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. clozapine	No significant difference in mean hospital bed days (1 RCT).
	Haloperidol vs. olanzapine	No significant difference in mean hospital bed days or rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (3 RCTs).
	Haloperidol vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (2 RCTs).
	Perphenazine vs. olanzapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine	Significant difference favoring olanzapine for number of active workers (i.e., work for pay) (1 RCT). No difference in impairment in household or work activities (1 RCT).

KQ = Key Question; RCT = randomized controlled trial

KQ3: Medication-Associated AEs and Safety

The findings for the AEs that were deemed most clinically important are summarized in Table D. The SoE comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone); mortality (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. risperidone; thioridazine vs. clozapine and risperidone); diabetes mellitus (haloperidol vs. olanzapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone); and metabolic syndrome (haloperidol vs. clozapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone).

Two trials each provided data on mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole; no significant differences were found, although the length of followup of the trials for the latter comparison was only 24 hours. For metabolic syndrome, two trials provided data for haloperidol versus olanzapine and showed no significant difference in incidence of metabolic syndrome. The SoE for these comparisons was low, suggesting that further research may change the results and change our confidence in the results.

Data were also recorded for general measures of AEs and specific AEs by physiological system (e.g., cardiovascular, endocrine); these outcomes were not assessed for SoE. For general measures of AEs, significant differences were found in the incidence of patients with AEs and withdrawals due to AEs for several comparisons. Most often, the comparison included haloperidol, and the risk was consistently higher for the FGA. The most frequently reported AEs with significant differences were in the category of EPS, and they most often involved a

comparison with haloperidol. In the vast majority of cases, the SGA had the preferred AE profile for EPS.

We were unable to adequately examine persistence and reversibility of AEs due to the relatively short followup of the included studies: study followup periods averaged 8 weeks. It is unclear whether AE persistence and reversibility of several significant AEs could be reasonably examined during this time period (e.g., metabolic conditions, body mass index or weight, and cardiovascular measures).

Table D. Summary of the strength of evidence for medication-associated adverse events and safety (KQ3)

Adverse Event	Comparison	SoE	Summary (Number of Studies)
Mortality	Chlorpromazine vs. clozapine	Low	No significant difference (2 RCTs, length of followup: 52 and 208 wks)
	Haloperidol vs. aripiprazole	Low	No significant difference (2 RCTs, length of followup: 24 hrs for both)
Metabolic syndrome	Haloperidol vs. olanzapine	Low	No significant difference (2 RCTs, length of followup: 6 and 12 wks)

KQ = Key Question; RCT = randomized controlled trial; SoE = strength of evidence

KQ4: Other Outcomes

The findings for other outcomes are presented for each condition and comparison in Table E. We did not assess the SoE for outcomes in KQ4.

Results for other outcomes were available for 19 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. Few significant differences were found across the comparisons and outcomes examined. For all significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials). Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (one trial) and patient satisfaction (one trial). Risperidone was favored over haloperidol for relapse rates (six trials). Olanzapine was favored over perphenazine for time to all-cause medication discontinuation (one trial). Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (one trial each); perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (one trial each).

Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder. Significant differences were found for health-related quality of life in one trial comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score, and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.

Table E. Summary of the evidence for other outcomes (KQ4)

Comparison	Summary[a] (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses	
Chlorpromazine vs. clozapine	Significant difference favoring clozapine for response rates (3 RCTs). No difference in remission rates (2 RCTs).
Chlorpromazine vs. olanzapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. quetiapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. ziprasidone	No significant difference in response rates (1 RCT).

Table E. Summary of the evidence for other outcomes (KQ4) (continued)

Comparison	Summary[a] (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses	
Fluphenazine vs. olanzapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. quetiapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. risperidone	No significant difference in response rates (1 RCT).
Haloperidol vs. aripiprazole	No significant difference in response rates (5 RCTs) or medication adherence (1 RCT). Difference favoring aripiprazole for caregiver and patient satisfaction (1 RCT).
Haloperidol vs. asenapine	No significant difference in response rates (1 RCT).
Haloperidol vs. clozapine	No significant difference in relapse (1 RCT), response (2 RCTs) or remission (1 RCT) rates or patient satisfaction (1 RCT).
Haloperidol vs. olanzapine	Significant difference favoring olanzapine for response rates (14 RCTs) and remission rates (3 RCTs). No significant difference in medication adherence (1 RCT), patient insight into illness (1 RCT), or HRQoL (5 RCTs).
Haloperidol vs. quetiapine	No significant difference in response rates (6 RCTs), remission rates (1 RCT), or HRQoL (1 RCT).
Haloperidol vs. risperidone	Significant difference favoring risperidone for relapse rates (6 RCTs). No significant difference in remission rates (2 RCTs), response rates (16 RCTs), medication adherence (3 RCTs), patient satisfaction (1 RCT), or HRQoL (2 RCTs).
Haloperidol vs. ziprasidone	No significant difference in response rates (6 RCTs), remission rates (3 RCTs), or HRQoL (2 RCTs).
Perphenazine vs. aripiprazole	No significant difference in response rates (1 RCT) or HRQoL (1 RCT).
Perphenazine vs. olanzapine	No significant difference in HRQoL (1 RCT). Significant difference favoring olanzapine in time to all-cause medication discontinuation (1 RCT).
Perphenazine vs. quetiapine	No significant difference in HRQoL (1 RCT).
Perphenazine vs. risperidone	No significant difference in time to all-cause medication discontinuation (1 RCT) or HRQoL (1 RCT).
Perphenazine vs. ziprasidone	No significant difference in HRQoL (1 RCT).
Bipolar Disorder	
Haloperidol vs. aripiprazole	Significant difference in favor of haloperidol for relapse rates (1 RCT). No difference in remission (1 RCT) or response (2 RCTs) rates.
Haloperidol vs. olanzapine	No difference for relapse (1 RCT), response (1 RCT), or remission rates (1 RCT). Significant difference favoring haloperidol for HRQoL mental summary score (1 RCT). Significant difference favoring olanzapine for HRQoL physical summary score (1 RCT).
Haloperidol vs. quetiapine	No significant difference in response or remission rates (1 RCT).
Haloperidol vs. risperidone	No difference in response rates (1 RCT).
Haloperidol vs. ziprasidone	Significant difference favoring haloperidol for response rates (1 RCT). No difference for remission rates (1 RCT).

HRQoL = health-related quality of life; KQ = Key Question; RCT = randomized controlled trial
[a]Response rates were defined by authors of the primary studies and may have varied across trials.

KQ5: Subgroups

A total of 41 studies compared outcomes for predefined subgroups. Among the studies of patients with schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance. The race most often examined was Asian. No notable differences were observed for the subgroups compared with the overall findings.

The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar I and bipolar II. The results were consistent with the overall

findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.

Results in the Context of Other Research

The results of this review are similar in some respects to another recent systematic review of SGAs versus FGAs, although the present review is broader in scope in terms of medications included, patient populations, and outcomes.[9] There were a number of methodological differences between the previous review and this one. The previous review included antipsychotics not approved by the FDA, restricted the analysis to only double-blinded trials, included only studies examining optimum SGA dosage and oral route of administration, and pooled data across efficacy outcome measures. The differences in the methodologies may have led to slightly different conclusions regarding individual SGAs.

The previous review compared nine SGAs (six of which are included in this report) with FGAs for overall efficacy (total symptom scores); positive, negative, and depressive symptoms; relapse; quality of life; EPS; weight gain; and sedation. The authors reported that the overall efficacy of the FDA-approved SGAs clozapine, olanzapine, and risperidone was better than that of FGAs. In terms of global ratings and total symptom scores, we found that clozapine was more efficacious than chlorpromazine but not haloperidol. We found that olanzapine performed better than haloperidol on one of the three total symptom scores assessed. We found no differences between haloperidol and risperidone for the five total symptom scores reported. The previous review found that SGAs were not superior to FGAs regarding the negative symptoms. We found no difference in negative symptoms for haloperidol versus clozapine; however, we found evidence that olanzapine was more efficacious than haloperidol for negative symptoms, whereas the evidence for risperidone compared with haloperidol was mixed. In general, the findings for AEs were consistent between reviews, showing poorer safety profiles with respect to EPS for FGAs (specifically haloperidol) and more weight gain among the SGAs (in particular, olanzapine and risperidone).

One of the unique features of our review was the SoE assessments, which provide information on how confident we can be in the results of existing studies and how likely it is that the estimates of treatment effects will change with future research. In most cases, the SoE was insufficient or low, highlighting the likelihood that future research will change the estimates of effect and the need for a stronger evidence base to inform clinical practice.

Applicability

This report included studies that compared an individual FGA with an individual SGA. Placebo-controlled studies or studies comparing an FGA versus another FGA or an SGA versus another SGA were not included. Therefore, the evidence is focused on the comparative effectiveness of FGAs versus SGAs, but not on their effectiveness and safety compared with placebo or other active agents. Overall, there were 20 head-to-head comparisons across the relevant studies; however, within most comparisons there were few studies.

The focus of our review was adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, or bipolar disorder. The average age across studies ranged from 21 to 50 years (median = 37 years [IQR, 33 to 41]). Most studies were highly selective in patient enrollment and included patients who (1) met strict diagnostic criteria for case definition, (2) had few comorbidities, and (3) used few or no concomitant medications. Older adults and the most seriously ill patients were underrepresented. Such highly selective criteria may increase the

likelihood of drug benefit and decrease the likelihood of AE occurrence. Almost half the studies involved hospitalized patients (inpatient treatment) (62 of 125 studies) or mixed inpatient and outpatient populations (26 studies); relatively few studies examined only outpatient treatment populations (19 studies). As such, we judge the results of this report to be applicable to patients in outpatient and inpatient treatment settings.

Another factor that restricts the applicability is the limited duration of followup. Despite our efforts to identify long-term safety data from observational studies, only two retrospective cohort studies provided data for the minimum 2-year followup period.

Limitations of Existing Evidence

Inconsistency in treatment comparisons, outcomes, outcome measurement, and patient populations across studies makes it difficult to draw firm clinical conclusions. Few studies compared the same antipsychotic medications and dosage using similar measures; various scales and surrogate measures were used to assess efficacy for different outcomes and AEs. Consensus is needed regarding outcomes and measures used to assess outcomes. Additionally, functional outcomes and symptomatic outcomes (e.g., sedation, restlessness) were rarely and unequally reported throughout the trial reports, even though these outcomes are often vital to patient compliance.

A key limitation and challenge in synthesizing and interpreting this body of evidence is the issue of heterogeneous patient populations across and within studies, which is in part driven by the complex nature of these disorders and their course over time. The studies we included had very mixed populations with respect to disorder subtypes, comorbid drug or alcohol use, treatment resistance, and number of previous episodes. These variables may create differential response to treatment, and this has been the basis for recommendations around personalized medicine in this area.[8] We conducted extensive subgroup and sensitivity analyses to explore these varying features. The results of subgroup analyses should be interpreted as hypothesis generating rather than hypothesis confirming. Our findings may provide some information to make treatment decisions for individual patients but need to be confirmed in future research.

An additional limitation and challenge of synthesis in this area is that characteristics of the research may have changed over time, including drug doses (e.g., lower doses of FGAs in more recent studies) and patient populations (e.g., fewer patients already exposed to FGAs or proven treatment resistant to FGAs in recent studies).

An important limitation of this review and other systematic reviews is the design and quality of the primary included studies. The majority of studies providing data for this report were RCTs (n = 123); however, most were designed as superiority trials, often with an a priori hypothesis that the SGA would be more efficacious.[10] The individual studies and, in many cases, the pooled results may not have sufficient power to detect equivalence or noninferiority between drugs. Further, all of the included trials had an unclear risk of bias (n = 78, 63 percent) or high risk of bias (n = 45, 37 percent). Of note, few trials (n = 20) reported blinding study investigators and participants (26 percent had unclear reporting), which is important in interpreting the results because lack of blinding has been shown to produce exaggerated treatment effects.[9]

Future Research

More longitudinal research is needed on the long-term comparative effectiveness of FGAs versus SGAs. Only two cohort studies were identified for this review that examined serious AEs with long-term antipsychotic use; these studies examined only two serious events: tardive

dyskinesia and mortality rates. The SoE for these AEs was insufficient to draw conclusions. Studies examining the naturalistic and long-term efficacy, and particularly the safety, of antipsychotics over the course of several years and across a number of important AEs are required. Further, consensus is needed on the most important comparisons of FGAs versus SGAs for future studies; the most frequent FGA in the studies to date was haloperidol.

Short- and long-term evaluations of the effectiveness of FGAs and SGAs with patient subpopulations, including patients with medical and neurological comorbidities, are needed. Further, there is a need for studies investigating how drug dose, age, and other factors, such as comorbidities, influence the occurrence of serious AEs, which would help estimate possible risks in specific patient populations.

Future studies should examine functional naturalistic outcomes that are important to patients. These outcomes include health-related quality of life and other patient-reported outcomes, relationships, academic and occupational performance, and legal interactions.

Conclusions

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness and safety of individual FDA-approved FGAs compared with individual FDA-approved SGAs. The report provides extensive details in terms of study characteristics and methodological features, which may help inform individual treatment decisions.

Numerous studies provided data on core illness symptoms; however, many different scales were used to assess outcomes, which limited the quantitative pooling of data. Few notable differences of clinical importance were identified. The SoE was low or insufficient for most comparisons, suggesting that future research is likely to change the results and change our confidence in the results.

Data on the relative effectiveness for functional outcomes, health care system utilization, and other outcomes were generally sparse. The variety of functional measures assessed across studies precluded firm conclusions regarding the overall effectiveness of individual drugs in terms of patient functioning. Few studies reported on health care system utilization or patient-important outcomes. Where health-related quality of life was assessed, no differences were found.

We included cohort studies with a minimum followup of 2 years in order to identify the AEs of most clinical importance, including diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. Only two studies with long-term followup were identified; hence, evidence on these important AEs is limited and urgently needed. A variety of AEs associated with numerous physiological systems were reported. The AEs most often reported involved EPS, which occurred more frequently for FGAs, particularly haloperidol, than for SGAs. Long-term longitudinal studies of at least 2-year duration are needed to detect important differences in the relative safety profile of individual FGAs and SGAs.

The evidence for important subgroups was limited. The most frequently examined subgroups were race and treatment resistance. There were no notable differences in outcomes for these subgroups compared with the overall results.

In summary, data on the comparative effectiveness of individual FGAs and SGAs precluded drawing firm conclusions for outcomes that are directly relevant to front-line clinical decisions. Overall, there were few significant differences of clinical importance. Outcomes potentially important to patients were rarely assessed. Finally, data on long-term safety are lacking and urgently needed.

References

1. Meltzer HY, Huang M. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res. 2008;172:177-97. PMID: 18772033.
2. Lopez-Gil X, Artigas F, Adell A. Unraveling monoamine receptors involved in the action of typical and atypical antipsychotics on glutamatergic and serotonergic transmission in prefrontal cortex. Curr Pharm Des. 2010;16(5):502-15. PMID: 19909228.
3. Aparasu RR, Bhatara V. Antipsychotic use and expenditure in the United States. Psychiatr Serv. 2006;57(12):1693. PMID: 17158480.
4. Ascher-Svanum H, Nyhuis AW, Stauffer V, et al. Reasons for discontinuation and continuation of antipsychotics in the treatment of schizophrenia from patient and clinician perspectives. Curr Med Res Opin. 2010;26(10):2403-10. PMID: 20812791.
5. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The Cochrane Collaboration; 2008.
6. Eden J, Levit L, Berg A, et al., eds. Finding What Works in Health Care: Standards for Systematic Reviews. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Board on Health Care Services. Washington: The National Academies Press; 2011.
7. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. Department of Epidemiology & Community Medicine, University of Ottawa, Canada. 2009. www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
8. Clark SL, Adkins DE, van den Oord EJ. Analysis of efficacy and side effects in CATIE demonstrates drug response subgroups and potential for personalized medicine. Schizophr Res. 2011;132(2-3):114-20. PMID: 121872442.
9. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31-41. PMID: 19058842.
10. Lieberman JA, Stroup TS. The NIMH-CATIE Schizophrenia Study: what did we learn? Am J Psychiatry. 2011;168(8):770-5. PMID: 121813492.

Introduction

Antipsychotic medications are used to treat and manage symptoms for several psychiatric disorders and are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as "typical antipsychotics," were developed in the 1950s. Second-generation antipsychotics (SGAs), also known as "atypical antipsychotics," emerged in the 1980s. To date, FGAs have been classified according to their chemical structure, which includes serotonin-dopamine antagonists and multi-acting receptor-targeted antipsychotics, whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists. There is ongoing research testing these proposed mechanisms of action within each class with respect to the neurobiology of different psychiatric disorders.[1,2]

According to findings from the 2004–2005 U.S. Medical Expenditure Panel Survey, an estimated 2 million adult patients in the United States were prescribed an antipsychotic medication; of which three-quarters of patients were taking a SGA.[3] In 2003, an estimated $2.82 billion was spent in the United States on these medications, with SGAs accounting for 93 percent of this expenditure.[3]

FGAs were first developed for the treatment of psychosis (e.g., schizophrenia). Since then, they have also been proven effective in the treatment of other conditions including acute mania, agitation, and bipolar disorder. Most FGAs are phenothiazine derivatives and are confounded by their varying degrees of dopamine (e.g., D1–D5), histamine, and cholinergic receptor antagonism. Today, there are 11 Food and Drug Administration (FDA)-approved and commercially available FGAs in the U.S., with chlorpromazine, perphenazine, and haloperidol being the most frequently prescribed (Table 1). The major differences between these three FGAs are their potency (low to high, respectively) and side-effect profiles.

The mechanisms of action and side-effects profiles of SGAs differ markedly from drug to drug. SGAs have been proven effective for treating a variety of psychiatric conditions by blocking the cerebral dopamine pathways. Currently, nine SGAs are FDA-approved and commercially available in the U.S., with quetiapine, risperidone, aripiprazole, and olanzapine being the most frequently prescribed (Table 1).[4]

Individuals taking an antipsychotic may stop taking their medication for a number of reasons, including side effects and lack of improvement in their symptoms.[5] As a result, ongoing evaluations of drug efficacy and models of patient decision-making are essential.

The disconnect between the research findings of well-known studies CUtLASS 1, CATIE, recent meta-analyses (showing few significant differences between FGAs and SGAs), individual efficacy trials (pharmaceutical industry trials favoring SGAs), and the prescribing patterns of clinicians (favoring SGAs) make this review an important step toward bringing together rigorous evidence for making clinical decisions and shaping health care policy.

This comparative effectiveness review (CER) provides a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs. In contrast to previous reviews this CER focuses on comparisons of individual medications rather than drug classes. This topic is important and timely given the ongoing debate about the comparative benefits and harms of FGAs and SGAs.[6] Moreover, the focus of this report complements other recent reviews investigating different SGAs,[7] the off-label use of antipsychotics,[8] and FGAs versus SGAs in the pediatric population.[9] The focus of this report is adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar

disorder. This age group is the normal demographic in which these illnesses have been shown to be prevalent; these illnesses are discussed in more detail in the sections that follow.

Table 1. List of antipsychotics included in the comparative effectiveness review*

First-Generation Antipsychotics	Second-Generation Antipsychotics
	Monotherapy
Chlorpromazine	Aripiprazole
Droperidol	Asenapine
Fluphenazine	Clozapine
Haloperidol	Iloperidone
Loxapine	Lurasidone
Perphenazine	Olanzapine
Pimozide	Paliperidone
Prochlorperazine	Quetiapine
Thioridazine	Risperidone
Thiothixene	Ziprasidone
Trifluoperazine	Combination therapy
	Olanzapine plus fluoxetine

* Multiple formulations (e.g., extended-release) are available for some antipsychotics. All drugs are FDA-approved and currently available at the time of this report.

Schizophrenia and Related Psychoses

Schizophrenia is a heterogeneous syndrome that includes disturbances in language, perception, cognition, social relatedness, and volition.[10] Symptoms include positive (i.e., delusions and hallucinations), negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation) symptoms. Onset of symptoms typically occurs in late adolescence or early adulthood, with approximately 0.4 to 0.6 percent of the population affected worldwide.[11] Antipsychotic medications represent the first-line treatment for patients with schizophrenia and have been the mainstay treatment since the 1950s. The American Psychiatric Association (APA) currently recommends that selection of an antipsychotic medication should be based on a patient's previous responses to the drug and its side-effect profile.[12]

In the treatment of schizophrenia, FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors.[13] This mechanism, however, may lead to a variety of extrapyramidal symptoms (EPS) (e.g., tremor, slurred speech, akathisia, and dystonia), some of which appear after long-term exposure (e.g., tardive dyskinesia).[14,15] Although these antipsychotics are effective against the positive symptoms of schizophrenia, they have been considered to be ineffective in treating negative symptoms.[16] Such symptoms particularly play a critical role in producing the severe social and vocational disabilities experienced by many patients with schizophrenia.[17]

The search for antipsychotic medications that manage both the positive and negative symptoms of schizophrenia led to the emergence of second-generation antipsychotic drugs. SGAs have been replacing FGAs as the treatments of choice. Although SGAs were developed to improve on the shortcomings of FGAs, they also have significant limitations in terms of side effects, including sedation, hypotension, weight gain, and sexual dysfunction.[18] SGAs have also been associated with metabolic side effects (e.g., elevated lipids and development of type II diabetes mellitus),[18] but it is unclear whether these are secondary to, independent of, or causative of weight gain. The long-term consequences of SGAs largely remain unknown.[19]

There is debate surrounding the efficacy of SGAs on negative symptoms, with several published reports indicating no clear advantage over FGAs.[17,20] Trials in which SGAs have been evaluated are criticized for 1) including patients with positive and negative symptoms, making it unclear whether a drug had direct effects, indirect effects, or both, on primary negative symptoms[20] and 2) deriving data on negative symptoms from short-term trials that focused on patients selected on the basis of positive symptoms (or, for longer-term trials, on the basis of clinical stability).[17] Recent findings from the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)[21,22] and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[23,24] found few differences in the effectiveness of SGAs and FGAs in patients with nonrefractory schizophrenia. Subsequent meta-analyses have generally confirmed these results[25] and have helped to provide a clearer picture of the comparative effectiveness of the two classes of antipsychotic medications.

Scales for Assessing the Core Symptoms of Schizophrenia

The most frequently used scales for measuring core illness symptoms in patients with schizophrenia are the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) scale, and Positive and Negative Symptom Scale (PANSS). Additionally, the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) are often used to gauge positive and negative symptoms in this patient population.

The BPRS is a 7-point scale for measuring psychiatric symptoms (e.g., depression, anxiety, hallucinations, and unusual behavior). Depending on the version, a total score of 18 to 24 points can be accumulated, with a higher score reflecting worse symptoms. The items on the scale are: somatic concern, anxiety, depression, suicidality, guilt, hostility, elated mood, grandiosity, suspiciousness, hallucinations, unusual thought content, bizarre behavior, self-neglect, disorientation, conceptual disorganization, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerisms, and posturing.

The CGI scale was developed for use in National Institute of Mental Health–sponsored clinical trials to provide a clinician-oriented assessment of the patient's global function before and after study medication is given. CGI scales are commonly used for measuring symptom severity (CGI–S), treatment response or improvement (CGI–I), and the efficacy of treatments (CGI–Efficacy Index). The former two scales are measured on a 7-point scale, and the latter is measured on a 4 x 4-point scale.

The PANSS is used for measuring symptom severity following a 45-minute clinical interview with the patient and reviewing relevant reports from family members and primary care hospital workers. Each of 30 symptoms is rated from 1 (absent) to 7 (extreme). Symptoms are grouped into three subscales: positive symptoms (i.e., delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness or persecution, and hostility), negative symptoms (i.e., blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking), and general psychopathology symptoms (i.e., somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

Bipolar Disorder

Bipolar disorder is characterized by severe fluctuations in mood, activity, thought, and behavior.[10] Bipolar I disorder involves one or more episodes of mania or mixed mood, which are associated with increased psychomotor activity, excessive social extroversion, decreased need for sleep, impulsivity, impairment in judgment, and grandiose mood. Patients may experience delusions, paranoid thinking, and extreme agitation. Bipolar II disorder is characterized by at least one hypomanic episode and at least one major depressive episode. The prevalence of bipolar disorder is 0.4 to 1.6 percent in community samples and has an average age of onset of 20 years.[10] The APA (2002)[26] recommends the following treatment plan: 1) polytherapy (lithium or valproate in conjunction with an antipsychotic) for severe manic or mixed episodes; and 2) monotherapy (lithium, valproate, or an antipsychotic) for less ill patients. The APA recommendations state that SGAs are preferred over FGAs because of their side-effect profile.[26]

Commonly used scales for measuring core illness symptoms in bipolar disorder are the Clinical Global Impression–Bipolar version (CGI–BP), Global Assessment Scale (GAS), and Young Mania Rating Scale (YMRS). CGI–BP was developed for rating the severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness. GAS is a single-item scale for evaluating overall patient functioning (i.e., 1 (sickest person) to 100 (healthiest person) divided into 10 equal intervals). The YMRS scale is an 11-item, multiple-choice, diagnostic questionnaire for psychiatrists to measure the severity of manic episodes. Items include elevated mood, increased motor activity, sexual interest, sleep, irritability, speech (rate and amount), thought disorder, thought content, aggressive behavior, appearance, and insight.

Key Questions

From mid-December 2009 to mid-January 2010, the draft Key Questions (KQs) for this report were posted for public comment on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site. The Technical Expert Panel, Evidence-based Practice Center (EPC), and AHRQ reviewed the comments that we received. We made the following changes based on this feedback:

1. The terminology of "typical" and "atypical" antipsychotics was changed to "first-generation" and "second-generation" antipsychotics in the title and throughout the KQs, protocol, and report.
2. The focus of KQ1 was on the core symptoms and KQ2 was on functional outcomes.
3. Study inclusion in the CER was not limited by drug dosage.
4. Individual antipsychotic medications, rather than a particular class, were set as the interventions and comparators for this review.
5. Relapse and remission rates were included as key outcomes.
6. The search strategy was expanded to include studies from 1950 onward to capture all studies that compared FGAs with SGAs.
7. The search strategy was expanded to include randomized trials, cohort studies (for serious adverse events (SAEs); see point 8 below), and systematic reviews that may answer the KQs.
8. To capture data on long-term SAEs, the inclusion criteria were modified to include cohort studies that compared FGAs with SGAs, had a followup period of at least 2 years, and

presented data on at least one SAE as determined by the Technical Expert Panel (i.e., type II diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).

9. We added the following outcomes of interest:
   Key symptoms:
   - Core symptoms, including maintenance of mood stability (particularly for bipolar disorder).
   - Measures for bipolar disorder symptoms: YMRS, MADRS, and CGI–BP.

   Adverse events (AEs):
   - Weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, and lipids and the risk of developing diabetes).

   Other outcomes:
   - Comorbidity: endpoints of victimization, homelessness, and substance abuse.
   - Patient-reported outcomes.
   - Ability to obtain and retain employment and succeed in job duties.
   - Concomitant use of other medications, especially those used to treat EPS.
   - Patient preferences.
10. Proposed subgroup analyses were revised to include dosage, length of followup, previous exposure to antipsychotics, treatment of a first episode versus treatment in the context of previous episodes, and treatment resistance.

The final revised KQs are as follows:

KQ 1: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?

Population: Adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder.
Interventions: Any commercially available FDA-approved FGA.
Comparators: Any commercially available FDA-approved SGA.
Outcomes: Improvement or change in disorder-specific and nonspecific symptoms.
The following symptoms are included for each disorder:

1. Core illness symptoms for schizophrenia or related psychoses: positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation).
2. Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

Timing: All time points; the last time point will be assessed if data on multiple time points are provided.
Settings: All settings, including treatment in hospital and outpatient settings.

KQ 2: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes:

1. Functional outcomes include any of the following: employment or personal earnings, social relatedness or functioning, encounters with the legal system, sexual function or dysfunction, functional capacity, and living situation.
2. Health care system utilization include: time to hospitalization or rehospitalization because of mental illness and all other causes, rates of hospitalization or rehospitalization, mean hospital bed days, length of hospitalization stay, rates of emergency department visits, attendance in day care programs, and use of ancillary caseworkers.

Timing: See KQ1 above.
Settings: See KQ1 above.

KQ 3: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated adverse events and safety?

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes: Disorder-specific and -nonspecific AEs:

1. Overall AEs.
2. Specific AEs:
    a. *Major:* mortality, cerebrovascular disease–related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide.
    b. *General:* EPS, weight gain, agitation, constipation, sedation, elevated cholesterol, AEs related to prolactin elevations, galactorrhea or bloody galactorrhea, weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).
3. Study withdrawals and time to withdrawal because of AEs.
4. Persistence and reversibility of AEs.

Timing: See KQ1 above.
Settings: See KQ1 above.

KQ 4: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for other outcomes?

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes:

1. Relapse and remission rates.
2. Medication adherence and persistent use (and associated dosing and time to discontinuation of treatment).
3. Patient insight into illness.
4. Health-related quality of life.
5. Patient satisfaction.
6. Comorbidity: endpoints of victimization, homelessness, and substance abuse.
7. Patient-reported outcomes.
8. Ability to obtain and retain employment and succeed in job duties.
9. Concomitant use of other medications, especially those used to treat EPS.
10. Patient preferences.

Timing: See KQ1 above.
Settings: See KQ1 above.

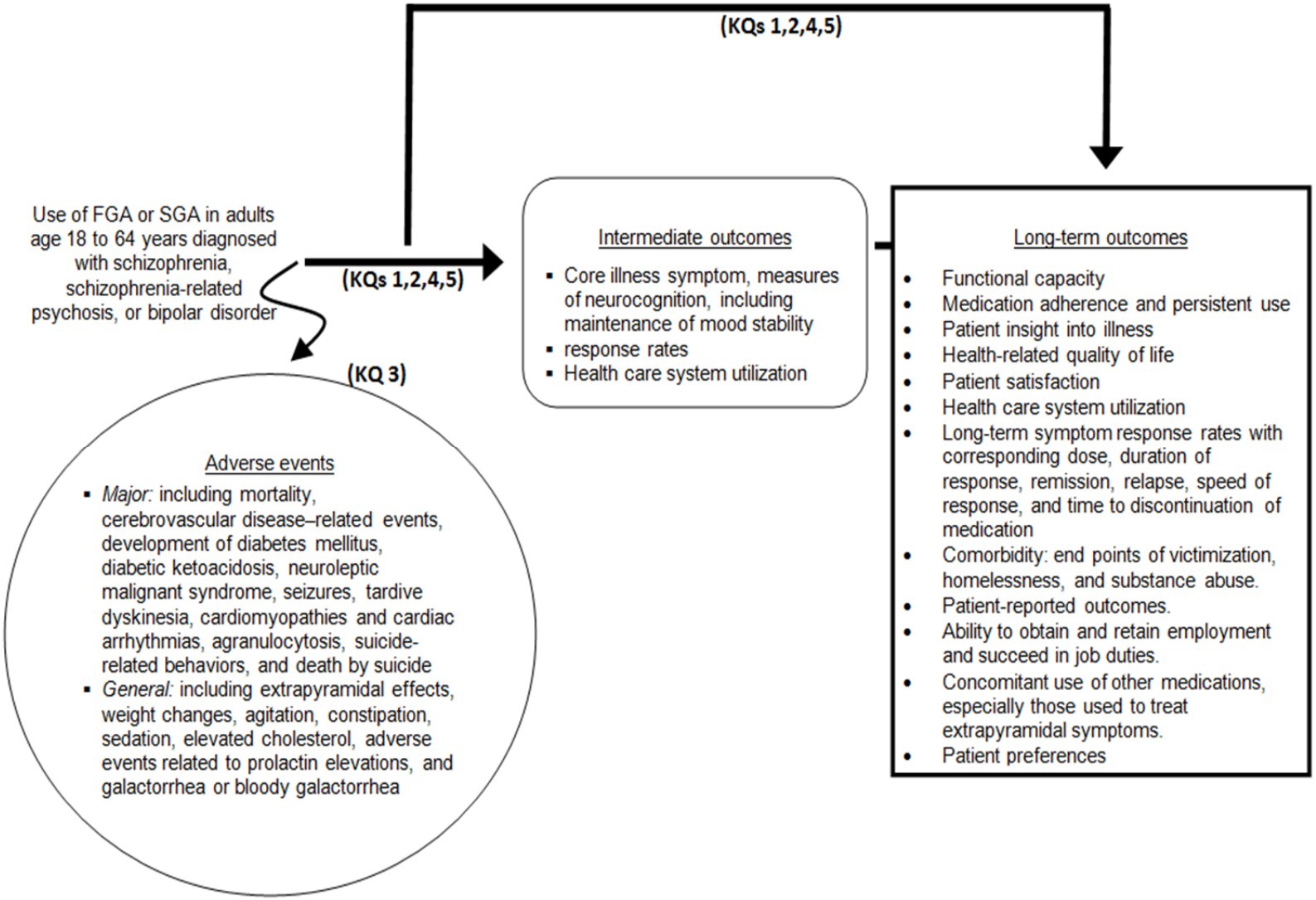
KQ 5: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?

1. Disorder subtypes.
2. Sex.
3. Age group (18–35 years, 36–54 years, 55–64 years).
4. Race.
5. Comorbidities.
6. Drug dosage.
7. Followup period.
8. Previous exposure to antipsychotics.
9. Treatment of a first episode versus treatment in the context of previous episodes.
10. Treatment resistance.

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes: Core illness symptoms (see KQ1), functional capacity and decreasing health care-system utilization (see KQ2), AEs (see KQ3), or other outcomes (KQ4).
Timing: See KQ1 above.
Settings: See KQ1 above.

Figure 1 depicts the KQs within the context of an analytic framework.

Figure 1. Analytic framework for the comparative effectiveness of FGAs and SGAs



FGA = first-generation antipsychotic; KQ = Key Question; SGA = second-generation antipsychotic

Methods

This chapter describes the a priori methods we used to synthesize the evidence on the comparative effectiveness of first-generation (FGAs) and second-generation antipsychotics (SGAs) in the adult population. We describe the topic refinement process for developing the Key Questions (KQs). We outline the literature search strategy, the selection process for identifying relevant articles, the process for extracting data from eligible studies, the methods for assessing the methodological quality of individual studies and for grading the strength of evidence of the overall body of evidence, and our approach to data analysis and synthesis. In general, we followed methodologically rigorous methods for systematic reviews as described in recent standards documents.[27,28] and the EPC Methods Guide (www.effectivehealthcare.ahrq.gov/methodsguide.cfm/).

Topic Refinement and Technical Expert Panel

Our EPC was commissioned to conduct a preliminary literature review to gauge the availability of evidence and to draft the key research questions for a full comparative effectiveness review (CER). Investigators from our EPC developed the KQs in consultation with AHRQ, the Scientific Resource Center, and a Technical Expert Panel. AHRQ posted the initial questions on their Web site for public comment for a period of 1 month. After reviewing the public comments, we revised the KQs, and AHRQ approved the final questions.

We invited the Technical Expert Panel to provide content and methodological expertise throughout the development of the CER.

Literature Search Strategy

Our research librarian conducted comprehensive searches in the following electronic databases from 1950 to July 2011: Ovid's MEDLINE®, Embase, PsycINFO, International Pharmaceutical Abstracts, Ebscohost CINAHL, ProQuest® Dissertations and Theses–Full Text, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus™ (Appendix A–1 to A–5). We also searched the U.S. National Library of Medicine's TOXLINE® database and the MedEffect™ Canada Adverse Drug Reaction Database from 1950 to July 2010 in order to identify additional data on adverse events (AEs). We restricted the searches to English-language randomized controlled trials (RCTs), nonrandomized controlled trials (nRCTs), cohort studies, and review articles examining adults.

We selected search terms by scanning search strategies of systematic reviews on similar topics and by examining index terms of potentially relevant studies. The detailed search strategies for each database are presented in Appendix A. We conducted the original searches between July 15 and July 22, 2010, with periodic updates of the searches up to July 2011.

We hand searched conference proceedings of the American Psychiatric Association (APA) (2008–2010), the International College of Neuropsychopharmacology (2008–2010), and the International Society for Bipolar Disorders (2008–2010). To identify unpublished studies and studies in progress, we searched clinical trials registers, contacted experts in the field, and contacted authors of relevant studies. We reviewed the reference lists of reviews and guidelines to identify potential studies for inclusion. We searched for articles citing the studies that met the inclusion criteria for this review using Scopus™ Citation Tracker. We searched grey literature by searching the U.S. Food and Drug Administration (FDA) Web site for relevant documents, and

soliciting "Scientific Information Packets" from manufacturers of the FGAs and SGAs through the Scientific Resource Center. We collected these materials asking the manufacturers for any material (published or unpublished) related to the KQs of the review. We made manufacturers aware that any materials submitted may become public through the Freedom of Information Act. The materials received from several manufacturers was reviewed for potential inclusion.

We used a Reference Manager® 11.0.1 (Thomson Reuters, Carlsbad, CA) bibliographic database to manage the results of our literature searches.

Criteria for Study Selection

Study selection was based on an a priori set of inclusion and exclusion criteria for study design, patient population, interventions, comparators, and outcomes (Table 2). We screened the results of our searches using a two-step process. First, two reviewers independently screened the titles and abstracts (level 1 screening) to determine if an article met the broad inclusion or exclusion criteria for study design, population, interventions, and comparators. We rated each citation as: "include," "exclude," or "unclear." Records rated as "include" or "unclear" were advanced to level 2 screening. For full-text screening (level 2 screening), two reviewers independently reviewed each retrieved study using a standardized screening form (Appendix B) that was developed and piloted by the review team. We resolved discrepancies through discussion and consensus or by third-party adjudication. Reviewers were not masked to the study authors, institution, or journal.[29]

We included studies that included at least 80 percent of patients from the adult population (18–64 years). Polypharmacy is common in clinical practice; therefore, we did not exclude studies examining patients taking other medications from the CER. Studies that included both patients with schizophrenia and patients with bipolar disorder, but did not provide separate results for these two conditions, were included only for the AEs section (KQ3). To be included, cohort studies were required to have a followup period of at least 2 years and present data on at least one serious adverse event (SAE), as determined by the Technical Expert Panel (i.e., type II diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).

Table 2. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Publication type	English language, full-text publications from 1950 to present	Non-English language publications Conference abstracts
Study design	RCTs, nRCTs, and prospective and retrospective cohort studies	Observational study designs with no comparison group (e.g., case reports, case series, and cross-sectional studies) or case-control studies
Participants	Adults (age 18 to 64 years) with schizophrenia or related psychoses or bipolar disorder	Pediatric population (aged <18 years) Geriatric population (aged >64 years)
Interventions	Any currently available FDA-approved FGA (Table 1)	Currently unavailable or non-FDA-approved FGA or other interventions
Comparators	Any currently available FDA-approved SGA (Table 1)	Currently unavailable or non-FDA-approved SGA, placebo, or other interventions

Table 2. Inclusion and exclusion criteria (continued)

	Inclusion Criteria	Exclusion Criteria
Outcomes	Outcomes listed in the KQ; cohort studies must report on ≥1 SAE	None of the a priori identified outcomes were available from the trial report or communication with the study's corresponding author
Timing	All followup periods for trials; cohort studies ≥2 years followup	Cohorts with <2 years followup
Setting	All settings	NA

FDA = Food and Drug Administration; FGA = first-generation antipsychotic; KQ = Key Question; NA = not applicable; nRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SAE = serious adverse event; SGA = second-generation antipsychotic

Assessment of Methodological Quality

We assessed the risk of bias of RCTs and nRCTs using the Cochrane Collaboration's Risk of Bias tool.[27] We assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale.[30] A priori, the research team developed decision rules regarding application of the tools.

For RCTs and nRCTs, we performed a domain-based risk of bias assessment according to the principles of the Risk of Bias tool. The domains were: (1) sequence generation (i.e., was the allocation sequence adequately generated?); (2) allocation concealment (i.e., was allocation adequately concealed?); (3) blinding of participants, personnel, and outcome assessors (i.e., was knowledge of the allocated intervention adequately prevented during the study?); (4) incomplete outcome data (i.e., were incomplete outcome data adequately addressed?); (5) selective outcome reporting (i.e., were reports of the study free of suggestion of selective outcome reporting?); and (6) other sources of bias (i.e., was the study apparently free of other problems that could put it at a high risk of bias?). Other sources of bias included baseline imbalances and appropriateness of crossover design. Each domain was rated as having "low," "unclear," or "high" risk of bias.

The overall assessment was based on the responses to individual domains.[27] In accordance with the guidance from the Cochrane Handbook for Systematic Reviewers, if one or more of the individual domains had a high risk of bias, we rated the overall risk of bias as high. We rated the overall risk of bias as low only if all components were assessed as having a low risk of bias. The overall risk of bias was unclear for all other situations.

The Newcastle-Ottawa Scale, used to assess the quality of cohort studies, is comprised of eight items that evaluate three broad domains: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the assessment of study outcomes. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars. We considered a total score of 7 to 9 stars to indicate high quality, 4 to 6 stars to indicate moderate quality, and 3 or fewer stars to indicate poor quality.

Two reviewers independently performed quality assessment of the included studies and resolved disagreements through discussion and consensus or third party adjudication, as needed.

Data Extraction

Two reviewers independently extracted published data using standardized data extraction forms in Microsoft Word and Excel (Microsoft Corporation, Redmond, WA; Appendix B) forms. We resolved discrepancies through discussion and consensus or by third-party

adjudication. We piloted the data extraction forms with three studies[31-33] and resolved any identified issues.

We extracted data on the following: general study characteristics (e.g., study design, inclusion and exclusion criteria, length of followup); population characteristics (e.g., age and sex); interventions and dosing regimens; numbers of patients allocated to relevant treatment groups; outcomes measured, and the results of each outcome, including measures of variability by relevant intervention arm. We also recorded the funding source, if reported. When relevant data for multiple followup or observation periods were reported, we extracted only the longest followup data. When studies incorporated multiple relevant treatment arms, we extracted data from all groups. We noted the specific intervention, dosage, and intervals of each intervention to determine if arms were clinically appropriate for pooling.

When there were multiple reports of the same study, we referenced the primary or most relevant study and extracted only additional data from companion reports. We contacted corresponding authors for data clarification and missing data. We imported all data into Microsoft Excel (Microsoft Corporation, Redmond, WA) for data management.

For dichotomous data, we extracted the number of participants with events and the total number of participants. For continuous outcomes, we extracted the mean with the accompanying measure of variance for each treatment group. We analyzed continuous data as post-treatment score or absolute difference (or change score) from baseline.[34] Since final scores and change scores can be mixed in a meta-analysis, change scores were not calculated, but extracted, when presented by the authors. Since many studies used multiple scales and scoring systems to measure the outcomes, therefore, in addition to summary data and measure of variance, we extracted the scale and the type of analysis used in the study. For all outcomes, we used the definitions as reported by the authors of individual studies. For response rates, when multiple definitions were provided by authors, we chose the lower percentage reduction levels in order to standardize data extraction across all studies.

For AEs, we extracted the number of participants experiencing events and the total number of participants. We did not extract continuous measures (e.g. severity of AEs or plasma levels) because the primary concern was to define the comparative differences in AE incidence rather than severity. We counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an AE. We did not extract count data. All adverse events reported in the primary publication and companion papers were extracted to allow for comparative effectiveness of the adverse events profiles of FGAs and SGAs.

When data were available only in a graphical format, we extracted data from the available graphs using the distance measurement tool in Adobe Acrobat 8 Professional (Adobe Systems Inc., San Jose, CA). When data were not available for the measure of variability for continuous outcomes, we calculated the variability from the computed p-value; if not available, we imputed the variability from other studies in the same analysis.

Data Analysis

We present evidence tables for all included studies and a qualitative description of results. We conducted meta-analyses to answer the KQs using Review Manager 5.01 (The Cochrane Collaboration, Copenhagen, Denmark).

We pooled binary data using the Mantel-Haenszel method and a random-effects model (DerSimonian and Laird).[35] For continuous outcomes, we used the inverse variance method and a random-effects model (DerSimonian and Laird).[35] We used Chi-square to test for significant heterogeneity reduction in partitioned subgroups; $p<0.1$ was considered to be significant. We generated forest plots for KQ1 when at least two trials provided evidence. For all other outcomes, we presented forest plots only if there were at least five included studies.

We combined RCTs and nRCTs in the meta-analyses. We synthesized cohort studies separately, as meta-analysis including both trials and cohort studies is controversial.[36] For continuous summary estimates where the same measure of analysis was used, we calculated the MD with 95% confidence intervals (CI). We reported dichotomous summary estimates as relative risk with accompanying 95% CI.

For KQ3, data are not presented separately for schizophrenia and related psychoses and bipolar disorder because AEs associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being administered.

We tested for heterogeneity using an I-squared (I^2) statistic and accompanying 95% uncertainty intervals.[37] Heterogeneity could not be estimated when only one study provided evidence for an outcome. We did not calculate uncertainty intervals around the I^2 statistic when less than three studies were pooled. If the lower uncertainty boundary for the I^2 had a value of 75 percent or greater, we considered this to represent substantial heterogeneity, thereby precluding pooling of studies. When there was substantial statistical heterogeneity in a meta-analysis, we explored heterogeneity in subgroup and sensitivity analyses and removal of outliers. The I^2 statistic was interpreted based on the guidance in the Cochrane Handbook for Systematic Reviews of Interventions.[27]

Variables that we considered important to explain heterogeneity included specific intervention details (e.g., type and quantity), study design, funding source, and risk of bias. In addition, we conducted sensitivity analyses on studies with imputed data to determine if the imputations had any effect on the effect estimate (i.e., the measure used to estimate the differences in effect of an intervention against a comparator) or heterogeneity. A priori subgroup analyses included disorder subtypes, sex, age group (18–35 years, 36–54 years, and 55–64 years), race, comorbidities, drug dosage, followup period, previous exposure to antipsychotics, treatment of a first episode versus treatment in the context of prior episodes, and treatment resistance.

When appropriate, we combined data across the available dosing arms before conducting the meta-analysis. We combined dichotomous arms by simple addition and combined continuous arms by calculating the pooled mean and standard deviation.

We did not include dichotomous data with zero values (i.e., no participant experienced an event) in meta-analyses because summary trial results were not estimable. However, we reported the results from these studies in the narrative synthesis for the relevant intervention.

We explored potential publication bias graphically through funnel plots for comparisons with at least 10 studies. Additionally, we quantitatively assessed publication bias using the Begg adjusted rank correlation test and Egger regression asymmetry test.[38]

When pooled estimates were available, we considered clinical significance to be at least a 20 percent improvement between interventions on an individual scale.

Grading the Strength of a Body of Evidence

We evaluated the overall strength of evidence (SoE) for key outcomes identified a priori by the clinical experts (i.e., core illness symptoms in the categories of positive symptoms, negative symptoms, general psychopathology, global ratings and total scores, and clinically important serious AEs: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome). We used the EPC GRADE[39] approach, which is based on the standard GRADE approach developed by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) Working Group.[40] We assessed the SoE for the key core symptom scales and AEs (Table 3) by examining four major domains: risk of bias (low, medium, or high), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct or indirect), and precision (precise or imprecise).

For each key outcome for each comparison of interest, we assigned an overall evidence grade based on the ratings for the individual domains. We graded the overall SoE as "high" (i.e., high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (i.e., moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect and may change the estimate); "low" (i.e., low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (i.e., evidence is either unavailable or does not permit estimation of an effect). When no studies were available for an outcome or comparison of interest, we graded the evidence as insufficient. We used the GRADEprofiler software (GRADE Working Group) and modified the results in accordance with the EPC GRADE. Two reviewers independently graded the body of evidence and resolved disagreements through discussion.

Table 3. Outcomes assessed by GRADE*

Key Question	Outcome Category	Outcomes and/or Outcome Measures
KQ1 (Bipolar disorder)	Mood (anxiety)	Covi Anxiety Scale
	Mood (mania)	CARS–M, MRS, YMRS
	Mood (depression)	CDS–S, HAM–D, MADRS
	Sleep	Number of awakenings, sleep efficiency (%), stage REM (min), total REM activity, total sleep time (min)
	Global ratings and total scores	BRPS, CGI–BP, CGI–I, CGI–S, GAF, PANSS, PANSS-derived BPRS
KQ1 (Schizophrenia)	Positive symptoms	PANSS, SAPS
	Negative symptoms	PANSS, SANS
	General psychopathology	ABS, ACES, BDI, CABS, CDS–S, HAM–A, HAM–D, MADRS, MOAS, PANSS, PAS, YMRS
	Global ratings and total scores	BPRS, CGI–I, CGI–S, GAF, NOSIE–30, PANSS, PANSS-derived BPRS, SADS–C, SCL–90–R, SWBUN
KQ3 (conditions combined)	SAEs	Diabetes mellitus, major metabolic syndrome, mortality, tardive dyskinesia

* Based on outcomes available in the included studies; ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CARS–M = Clinician-Administered Rating Scale for Mania; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–BP = Clinical Global Impression–Bipolar; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HAM–D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; min = minute; MOAS = Modified Overt Aggression Scale; MRS = Mania Rating Scale; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale; PAS = Pscychotic Anxiety Scale; REM = rapid eye movement; SADS = Schedule for Affective Disorders and Schizophrenia; SAE = serious adverse event; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check List; SWBUN = Subjective Well-Being Under Neuroleptics scale; YMRS = Young Mania Rating Scale

Applicability

Applicability of evidence distinguishes between effectiveness studies, conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods, and efficacy studies.[41] The results of effectiveness studies are more applicable to the spectrum of patients in the community than efficacy studies, which usually involve highly selected populations. We assessed the applicability of the body of evidence following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Specific characteristics we examined included those related to patients (e.g., age, diagnostic criteria, severity of illness, comorbidities, concomitant medications, inpatient or outpatient status) and those related to study design (e.g., length of followup). We reported clinically important outcomes and participant characteristics in the results.

Results

This chapter reports on the results of our literature review and synthesis. First, we describe the results of our literature search and selection process. Description of the characteristics and methodological quality of the studies follow. For Key Questions (KQs) 1, 2, 4, and 5, we present the results of our analysis separately for schizophrenia and bipolar disorder and then by comparison. The findings for KQ3 are presented at the end of this section and are organized by comparison across both conditions. The results of all meta-analyses, including sample sizes, effect estimates, 95% confidence intervals (CI), and I-squared (I^2) statistics, are available in evidence tables for each comparison.

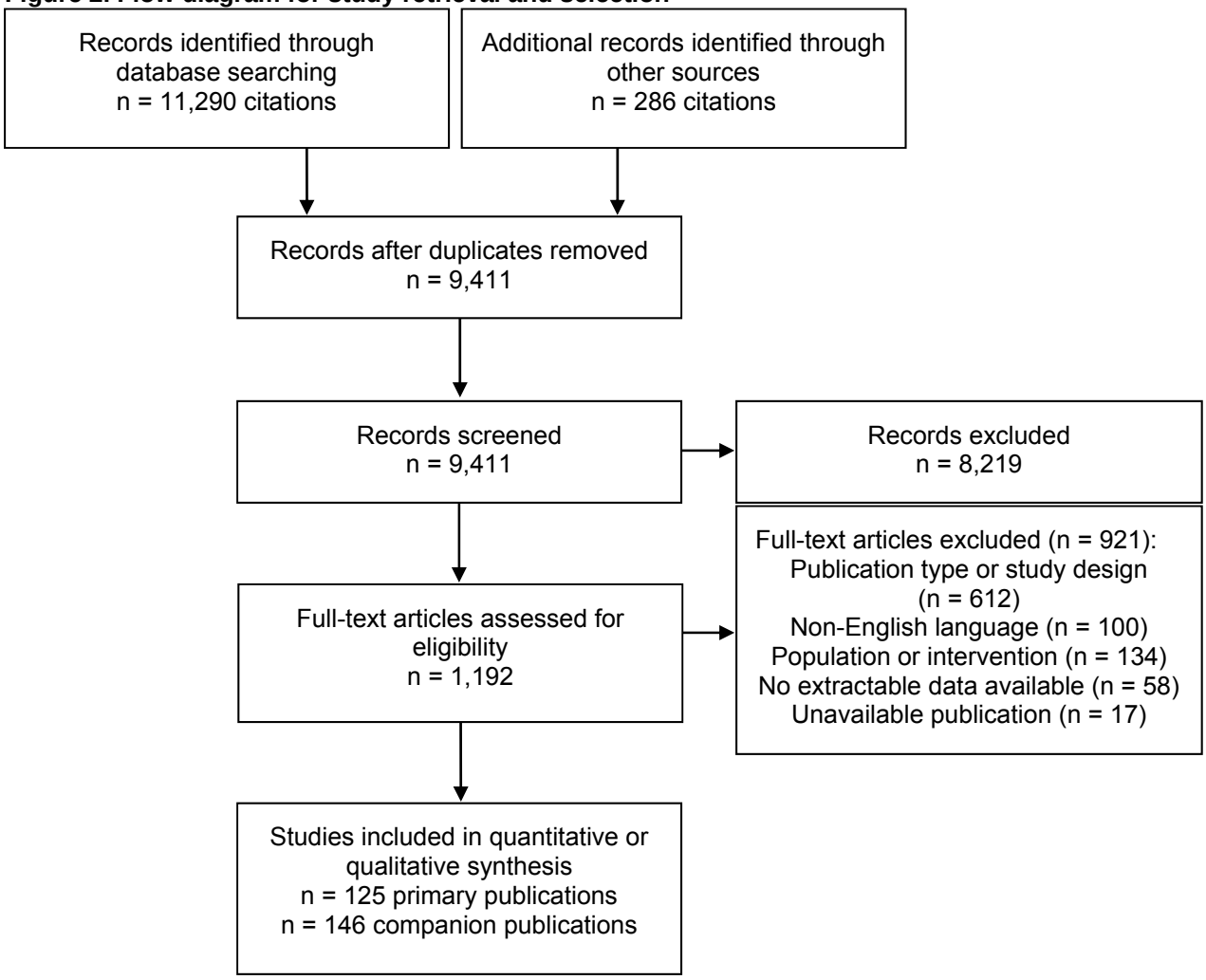
Several appendixes provide supporting information to the findings presented in this section. A list of citations for the excluded and unobtained studies and for companion studies are provided in Appendix C and D, respectively. Risk of bias assessments for trials are available in Appendix E and F, and quality assessments for cohort studies are available in Appendix G. A description of the general characteristics of the included studies and patient flow through the studies are provided in Appendix H and I, respectively. Forest plots for adverse events (AEs) (KQ3) and funnel plots for all comparisons and outcomes for which there were 10 or more studies are available in Appendix J and K, respectively. Appendix L contains evidence tables for core illness symptom subscales, composite outcomes, and measures of functional capacity (e.g., memory, recall, and motor skills). Appendix M contains evidence tables for subgroup and sensitivity analyses. Appendix N contains evidence tables for AEs.

Literature Search

All citations identified through electronic or hand searching and expert nomination were combined into a single database (Figure 2).[42] Of the 11,576 citations identified, 2,165 were duplicates and 9,411 were unique study reports.

Following level 1 screening, 8,219 were excluded, and 1,192 were further evaluated for inclusion. Of these, 125 primary publications[23,31-33,43-163] passed level 2 screening and were included in this comparative effectiveness review (CER). An additional 146 companion publications passed level 2 screening and are also included. The characteristics of the publications excluded at level 2 screening are presented in Figure 2 and Appendix C. The main reasons for exclusion were publication type (e.g., case-control study, observational study with followup <2 years, or review article), population characteristics (e.g., patient age and other psychiatric condition), use of antipsychotic medications that are not Food and Drug Administration (FDA)-approved or medications no longer available in the U.S., and no extractable data related to the outcomes of interest (e.g., ongoing studies).

Figure 2. Flow diagram for study retrieval and selection



Description of Included Studies

The 125 unique studies[23,31-33,43-163] included in this review are described in detail in the evidence tables found in Appendixes H and I. An overview is provided in Table 4, Table 5, and Table 6. The 146 companion articles that met our inclusion criteria were used for data that were not provided in the primary report. The primary studies were published between 1974 and 2010 (median = 2002 [interquartile range (IQR), 1998 to 2006]). The majority of the studies were randomized controlled trials (RCTs) (97 percent) and were conducted in multicenter settings (56 percent). Studies were most frequently conducted in North America (46 percent). The number of enrolled participants ranged from 10 to 95,632 (median = 86 [IQR, 36 to 300]). The mean age of study participants ranged from 21 to 50 years (median = 37 years [IQR, 33 to 41]). The length of followup ranged from <1 day to 22 years (median = 8 weeks [IQR, 6 to 26 weeks]). Seventy percent of studies (n = 88) had some form of support from the pharmaceutical industry.

A total of 113 studies examined adults with schizophrenia or related psychoses, 11 studies examined adults with bipolar disorder, and 1 study examined adults with either diagnosis. Overall, the studies examined 22 comparisons of individual first-generation antipsychotics (FGAs) and individual second-generation antipsychotics (SGAs) (Table 5 and Table 6).

Table 4. Characteristics of included studies

Category	Characteristic	Number of studies (%)
Study design	RCT	121 (96.8%)
	nRCT	2 (1.6%)
	Retrospective cohort study	2 (1.6%)
Number of centers	Multicenter	70 (56.0%)
	Single center	52 (41.6%)
	Two centers	3 (2.4%)
Setting	Inpatient	62 (49.6%)
	Outpatient	19 (15.2%)
	Mixed	26 (20.8%)
	Unclear or not reported	18 (14.4%)
Country	Africa	2 (1.6%)
	Asia	18 (14.4%)
	Australia	1 (0.8%)
	Europe	23 (18.4%)
	Middle East	1 (0.8%)
	North America	51 (40.8%)
	South America	5 (4.0%)
	International (including North America)	6 (4.8%)
	International (not including North America)	18 (14.4%)

nRCT = nonrandomized controlled trial; RCT = randomized controlled trial

Table 5. Drug comparisons available and number of studies for each comparison

	Aripipra-zole	Asena-pine	Cloza-pine	Olanza-pine	Quetia-pine	Risperi-done	Ziprasi-done
Chlorpromazine			13	1	1		1
Fluphenazine				2	1	1	
Haloperidol	10	1	11	37	12	43	10
Perphenazine	1			2	1	2	1
Trifluoperazine			1				
Thioridazine			1			1	

Table 6. Comparisons in the included studies by condition

Comparison	Schizophrenia (n)	Bipolar disorder (n)
Chlorpromazine vs. Clozapine	12	1
Chlorpromazine vs. Olanzapine	1	0
Chlorpromazine vs. Quetiapine	1	0
Chlorpromazine vs. Ziprasidone	1	0
Fluphenazine vs. Olanzapine	2	0
Fluphenazine vs. Quetiapine	1	0
Fluphenazine vs. Risperidone	1	0
Haloperidol vs. Aripiprazole	8	2
Haloperidol vs. Asenapine	1	0
Haloperidol vs. Clozapine	11	0
Haloperidol vs. Olanzapine	35	2
Haloperidol vs. Quetiapine	11	1
Haloperidol vs. Risperidone	39	5
Haloperidol vs. Ziprasidone	9	1
Perphenazine vs. Aripiprazole	1	0
Perphenazine vs. Olanzapine	2	0
Perphenazine vs. Quetiapine	1	0
Perphenazine vs. Risperidone	2	0
Perphenazine vs. Ziprasidone	1	0
Trifluoperazine vs. Clozapine	1	0
Thioridazine versus Clozapine	1	0
Thioridazine versus Risperidone	1	0

N = number; Vs. = versus

Methodological Quality of Included Studies

Two independent reviewers assessed the risk of bias of RCTs and nonrandomized trials (nRCTs) using the Risk of Bias tool and the methodological quality of cohort studies using the Newcastle-Ottawa Scale. Consensus ratings are presented in Appendix E through G. A summary of the overall quality by study design is presented below.

Randomized and Nonrandomized Controlled Trials

None of the 123 included trials[23,31-33,43-161] were rated as having a low risk of bias. The majority of the trials (n = 78)[23,31-33,43,44,46,47,49-56,59-61,64,66,67,70,72,74,78-81,84,85,87-89,93,94,96,97,99,101-110,112,113,115,117-127,131-134,138,143,145-147,150,153-155,158,160] were rated as having an unclear risk of bias due to under-reporting in the articles. The key potential biases in these studies were related to selection bias (i.e., random sequence generation and allocation concealment) and performance bias (i.e., proper blinding of participants and study personnel) (Appendix E and F). The remaining trials (n = 45)[45,48,57,58,62,63,65,68,69,71,73,75-77,82,83,86,90-92,95,98,100,111,114,116,128-130,135-137,139-142,144,148,149,151,152,156,157,159,161] were considered to have a high risk of bias. The key potential biases in these studies were related to attrition bias (i.e., incomplete outcome data) and performance bias (i.e., proper blinding of participants and study personnel) (Appendix E and F). A summary of the distribution of scores across the risk of bias domains is presented in Table 7.

Table 7. Distribution of risk of bias scores by domain for trials

Domain	High	Unclear	Low
Adequate sequence generation	3 (2.4%)	105 (85.4%)	15 (12.2%)
Allocation concealment	1 (0.8%)	116 (94.3%)	6 (4.9%)
Blinding	21 (17.1%)	83 (67.5%)	19 (15.4%)
Incomplete outcome data addressed	24 (19.5%)	32 (26.0%)	67 (54.5%)
Free of selective reporting	1 (0.8%)	3 (2.4%)	119 (96.7%)
Free of other bias	0 (0.0%)	20 (16.3%)	103 (83.7%)

Cohort Studies

Two cohort studies[162,163] met the inclusion criteria. The methodological quality of the cohort studies was good (8 of a possible 9 stars for both studies). Both of the studies received only 1 of a possible 2 points for measures taken to ensure the comparability of cohorts.

Schizophrenia (Key Questions 1, 2, 4, 5)

For schizophrenia, we included 113 studies that enrolled a total of 118,503 patients. The individual studies are described in Appendixes H and I. The results from the studies and pooled analyses are presented in Table 8 through Table 65. Within the forest plots, the studies are presented by year of publication. The following sections are organized by comparison and provide an overview of results according to the KQ: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For comparisons with more than one study, we highlight key points summarizing the overall findings prior to reporting detailed analyses.

For KQ1, the outcomes are grouped as follows: positive symptoms, negative symptoms, general psychopathology, global ratings, and total scores. Additionally, scores on subscales or composite scores, and functional capacity outcomes are presented in Appendix L. KQs 2 and 4

were grouped and are reported together throughout the results section. Within all KQs, comparisons are presented in alphabetic order by drug name.

Chlorpromazine Versus Clozapine

Key Points

- Nine RCTs comparing chlorpromazine with clozapine in patients with a range of illness severity were included; few studies examined the same outcomes.
- The most commonly reported outcome was total symptom score using the Brief Psychiatric Rating Scale (BPRS). Pooled results from six studies showed greater efficacy for clozapine, and the difference was considered clinically important (moderate strength of evidence (SoE)).
- Three trials assessed response rates and showed a significant difference favoring clozapine; two trials included treatment-resistant patients with followup between 6 and 12 weeks.
- Two trials assessed remission rates and found no significant difference; length of followup was 5 weeks (chronic schizophrenia) and 1 year (first-episode schizophrenia).
- The remaining outcomes were assessed in single trials; the majority showed no significant differences between antipsychotic effect.

Nine RCTs[63,87,94,109,153,154,157,158,161] (n = 765) compared chlorpromazine versus clozapine. The doses varied across the studies ranging from 50 to 1800 mg/d for chlorpromazine and 25 to 900 mg/d for clozapine. Key characteristics of the included trials and summary of results are presented in Table 8 and Table 9. All the trials included patients with schizophrenia. One trial[109] also included patients with schizophreniform disorder. Another trial[153] only included males with paranoid/hallucinatory or catatonic type schizophrenia. Two trials[87,94] were in patients considered to be treatment resistant; both studies assessed treatment resistance historically, whereas one of the studies[94] also confirmed treatment resistance with a run-in period. One study[109] focused on participants with first-episode schizophrenia. Three trials[87,109,161] included only Asian participants. Two trials[87,158] specifically excluded participants with drug or alcohol dependence.

The risk of bias was unclear for seven studies[87,94,109,153,154,158,161] and high for two studies.[63,157] Three studies had financial support from industry: in two studies[94,154] the industry sponsors were producers of both drugs being compared, whereas the third study[109] was sponsored by a company that produces clozapine. Duration of followup was ≤6 weeks for five studies,[94,153,154,157,158] between 6 weeks and 6 months for three studies,[63,87,161] and >6 months for two studies.[109,156]

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of included trials (Table 10).

Table 8.Characteristics of RCTs comparing chlorpromazine versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Claghorn et al. 1987[63] RCT (8 wks)	G1: CHL (50–1800mg/d); (76) G2: CLO (25–900mg/d); (75) Run-in phase: 2 wks	Sz w/ neurological reactions (either TD or EPS) induced by ≥2 prior AP	High, NR
Ekblom et al. 1974[153] RCT (5 wks)	G1: CHL (65–700mg/d); (21) G2: CLO (65–600mg/d); (20) Washout period: 2 wks	Male w/ acute Sz; relapsed or exacerbated chronic Sz cases of the paranoid/ hallucinatory or catatonic type	Unclear, NR
Gelenberg et al. 1979[154] RCT (8 wks)	G1: CHL (50–1800mg/d); (8) G2: CLO (25–900mg/d); (7) Washout period: 48 hrs	Sz not further defined	Unclear, Industry
Hong et al. 1997[87] RCT (12 wks)	G1: CHL (50–1800mg/d); (19) G2: CLO (25–900mg/d); (21) Run-in phase: 6 wks	Tx refractory Sz; symptom hx ≥6 mo	Unclear, Academic
Kane et al. 1988[94] RCT (6 wks)	G1: CHL (1000–1800mg/d); (142) G2: CLO (500–900mg/d); (126) Run-in phase: 6 wks	Hx of tx resistance; ≥3 periods of tx in ≤5 yrs w/ AP from 2 different classes; 6 wks w/ doses equivalent to 1000mg/d CHL without relief; no period of functioning ≤5 yrs;	Unclear, Multiple sources including industry
Lieberman et al. 2003[109] RCT (52 wks)	G1: CHL (≤600mg/d); (83) G2: CLO (≤400mg/d); (81)	Sz or schizophreniform disorder; symptoms <60 mo; no prior AP tx	Unclear, Industry
Rinieris et al. 1980[157] RCT (6 wks)	G1: CHL (50–100mg/d); (16) G2: CLO (50–100mg/d); (5) Run-in phase: 1 wk	Sz not further defined	High, NR
Shopsin et al. 1979[158] RCT (5 wks)	G1: CHL (50–1600mg/d); (12) G2: CLO (25–900mg/d); (13) Washout period: ≥1 wks	Chronic Sz; recent acute exacerbation necessitating involuntary hospitalization; no spontaneous remission	Unclear, NR
Singer et al. 1974[161] RCT (40 d)	G1: CHL (50–600mg/d); (20) G2: CLO (50–600mg/d); (20) Washout period: 2 wks	Acute Sz	Unclear, NR

AP(s) = antipsychotic(s); CHL = chlorpromazine; CLO = clozapine; D = days; EPS = extrapyramidal symptoms; G = group; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; No. = number; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; TD = tardive dyskinesia; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

One trial[87] (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d); there was no significant difference in positive symptoms based on the Positive and Negative Symptom Scale (PANSS) (Table 9). The SoE was graded insufficient (Table 10).

Negative Symptoms

One trial[109] (n = 164) of treatment-naïve patients with schizophrenia or schizophreniform disorder compared chlorpromazine (≤600 mg/d) with clozapine (≤400 mg/d) and reported no significant difference for negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS) (Table 9). The SoE was graded as insufficient (Table 10).

General Psychopathology

One trial[87] (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and found no significant difference for PANSS (general psychopathology) (Table 9). The SoE was graded as insufficient (Table 10).

Global Ratings and Total Scores

Seven trials[63,87,94,109,154,157,161] (n = 699) reported total scores using five unique scales (Table 9). All seven trials reported total scores based on the BPRS. Two trials[87,94] were in patients with treatment resistance. The dosages of chlorpromazine ranged from 50–1800 mg/d and clozapine from 25–900 mg/d.

Pooled results are not reported due to considerable heterogeneity among the included trials (I^2 = 90 percent) (Appendix M, Table 94). One trial[109] showed an effect in the opposite direction to the other studies: the point estimate favored chlorpromazine, although the difference between groups was not statistically significant. This trial was distinct from the other trials in that it specifically included patients with schizophreniform disorder and only those with a first episode, used relatively lower doses of both the FGA and SGA, and followed patients for 12 months. Removing this trial from the analysis reduced the heterogeneity to 20 percent.

Pooling of the remaining six trials showed a significant difference favoring clozapine (MD [mean difference] = 8.40; 95% CI, 5.92 to 10.88) (Table 9; Figure 3). This difference was considered to be clinically significant. The results of subgroup and sensitivity analyses showed some variation in the magnitude of effect based on population and study characteristics. A larger effect was observed for patients with treatment resistance and previous episodes, for trials with shorter followup periods, and for industry-funded trials. The effect in favor of clozapine was larger when higher doses of chlorpromazine were used (up to 1800 mg/d vs. 100 and 600 mg/day). Sensitivity analyses showed a larger effect when studies with imputed data were excluded, whereas no notable difference in effect was found based on risk of bias. Overall, the SoE for this outcome was graded as moderate (Table 10).

One trial,[94] (n = 268) in patients with a history of treatment resistance compared chlorpromazine (1000–1800 mg/d) with clozapine (500–900 mg/d) and reported Clinical Global Impression–Severity (CGI–S). The study found a significant difference favoring clozapine (Table 9). This difference was considered clinically significant; however, the SoE was graded as insufficient (Table 10).

One trial[109] (n = 164) in treatment-naïve patients comparing chlorpromazine (≤600 mg/d) with clozapine (≤400 mg) reported no significant difference based on the Clinical Global Impression–Improvement (CGI–I) and Global Assessment of Functioning (GAF) (Table 9). The SoE for these outcome measures was graded as insufficient (Table 10).

One trial[87] (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported no significant difference in PANSS (total) (Table 9). The SoE was graded as insufficient (Table 10).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

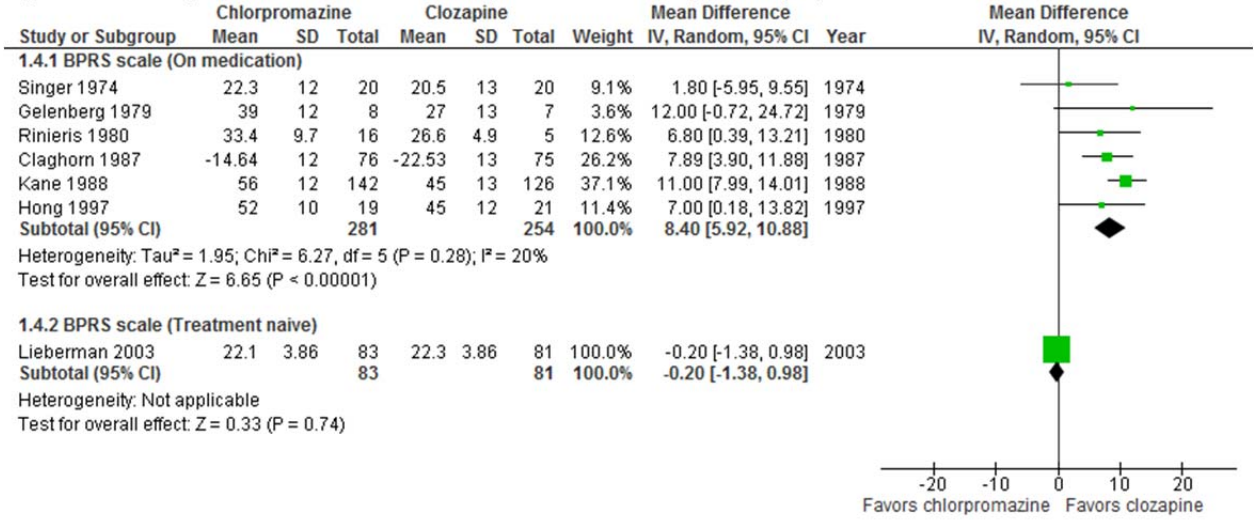
Health Care System Utilization

One trial[109] (n = 164) of treatment-naïve patients compared chlorpromazine (≤600 mg/d) with clozapine (≤400 mg) and found no significant differences in rates of hospitalization or rehospitalization (Table 9).

Other Outcomes. Three trials[87,94,154] (n = 323) in patients with schizophrenia, including those with treatment resistance,[87,94] compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported a significant difference favoring clozapine for response rates (Table 9).

Two trials[109,158] (n = 189) in treatment-naïve patients with schizophrenia or schizophreniform disorder[109] and chronic schizophrenics with an acute exacerbation necessitating involuntary hospitalization[158] compared chlorpromazine (50–1600 mg/d) with clozapine (25–900 mg/d). No significant differences were found in remission rates (Table 9).

Figure 3. Chlorpromazine versus clozapine – core symptoms (Sz) – Total score



BPRS = Brief Psychiatric Rating Scale; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; SD = standard deviation; Sz = schizophrenia

Key Question 5. Subgroups

Race

Three trials[87,109,161] (n = 244) were performed exclusively in Asian patients with schizophrenia and compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d). There was no significant difference for the PANSS (positive),[87] SANS,[109] PANSS (general psychopathology),[87] or global ratings and global ratings and total scores (BPRS,[87,109,161] CGI–I,[109] GAF,[109] and PANSS (total)).[87]

Sex

One trial[153] (n = 41) examined males with acute schizophrenia or relapsed or exacerbated chronic schizophrenia of the paranoid/hallucinatory or catatonic types. The trial compared

chlorpromazine (65–700 mg/d) with clozapine (65–600 mg/d); however, there was no extractable data for KQs 1, 2, or 4.

Treatment Naïve and Treatment of First Episode

One trial[109] (n = 164) in treatment-naïve patients compared chlorpromazine (≤600 mg/d) with clozapine (≤400 mg). No significant differences were reported for negative symptoms using SANS and global rating scores based on BPRS and CGI–I.

Treatment Resistance. Two trials[87,94] (n = 308) in patients with treatment resistance compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported a significant difference favoring clozapine for BPRS (MD = 10.22; 95% CI, 7.12 to 13.33) and CGI–S (MD = 0.90; 95% CI, 0.67 to 1.13). The differences were considered to be clinically significant. The differences on the PANSS (positive), PANSS (general psychopathology), and PANSS (total) were not significantly different between groups.

Table 9. Evidence summary table: chlorpromazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[87]	1	40	2.00 (-0.79, 4.79)	NE	ND
Negative Symptoms					
SANS[109]	1	164	2.00 (-2.66, 6.66)	NE	ND
General Psychopathology					
PANSS[87]	1	40	5.00 (-3.68, 13.7)	NE	ND
Global Ratings and Total Scores					
BPRS (On treatment)[63,87,94,154,157,161]	6	535	8.40 (5.92, 10.90)	20%	clozapine
BPRS (Treatment naïve)[109]	1	164	-0.20 (-1.38, 0.98)	NE	ND
CGI–I[109]	1	164	-0.20 (-0.63, 0.23)	NE	ND
CGI–S[94]	1	268	0.90 (0.67, 1.13)	NE	clozapine
GAF[109]	1	164	-1.00 (-12.1, 10.1)	NE	ND
PANSS (total)[87]	1	40	12.00 (-4.48, 28.5)	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[109]	1	164	0.70 (0.23, 2.11)*	NE	ND
Other Outcomes					
Response rates[87,94,154]	3	323	0.13 (0.06, 0.28)*	0%	clozapine
Remission rates[109,158]	2	189	0.66 (0.25, 1.74)*	72%	ND

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 10. Strength of evidence (GRADE): chlorpromazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
BPRS (on treatment)	6 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring clozapine)
CGI–I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence

Chlorpromazine Versus Olanzapine

One RCT[66] (n = 84) compared chlorpromazine (600–1200 mg/d) with olanzapine (12.5–25 mg/d) in patients with treatment-resistant schizophrenia (Table 11). There was no reported difference in core illness symptoms (negative symptoms, global ratings) and response rates between groups (Table 12). No other relevant outcomes were reported. The SoE for all reported outcomes was insufficient (Table 13).

Table 11. Characteristics of RCT comparing chlorpromazine versus olanzapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 1998[66] RCT (6 wks)	G1: CHL (600–1200mg/d); (42) G2: OLA (12.5–25mg/d); (42) Run-in phase: 6 wks	Tx resistant Sz; ≥2 periods of tx in ≤5 yrs with AP (≥2 classes, excluding HAL), at dosages ≥1000mg/d of CHL equivalents, for 6 wks	Unclear, Multiple sources

AP(s) = antipsychotic(s); CHL = chlorpromazine; D = days; G = group; HAL = haloperidol; Mg = milligrams; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Table 12. Evidence summary table: chlorpromazine versus olanzapine

Outcome or Subgroup	Studies	Partici-pants	Effect Estimate	I^2	Favors
Negative Symptoms					
SANS[66]	1	84	0.90 (-2.90, 4.70)	NE	ND
Global Ratings					
BPRS[66]	1	84	2.80 (-2.74, 8.34)	NE	ND
CGI–S[66]	1	84	0.10 (-0.29, 0.49)	NE	ND
Other Outcomes					
Response rates[66]	1	84	0.14 (0.01, 2.68)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable; SANS = Scale for the Assessment of Negative Symptoms

Table 13. Strength of evidence (GRADE): chlorpromazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Negative Symptoms						
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Chlorpromazine Versus Quetiapine

One RCT[121] (n = 201) compared chlorpromazine (75–750 mg/d) with quetiapine (75–750 mg/d) in patients with chronic or subchronic schizophrenia with an acute exacerbation or patients with schizophreniform disorder (Table 14). There was no reported difference in **response rates** between groups (Table 15). No other relevant outcomes were reported.

Table 14. Characteristics of RCT comparing chlorpromazine versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Peuskens et al. 1997[121] RCT (8 wks)	G1: CHL (75–750mg/d); (100) G2: QUE (75–750mg/d); (101) Washout period: 24 hrs	Acute exacerbation of chronic/ subchronic Sz, or schizophreniform disorder; not on depot AP	Unclear, Industry

AP(s) = antipsychotic(s); CHL = chlorpromazine; D = days; G = group; Hr(s) = hour(s); Mg = milligrams QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; Wk(s) = week(s)

Table 15. Evidence summary table: chlorpromazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Response rates[121]	1	201	0.81 (0.64, 1.02)*	NE	ND

* = binary outcome; I^2 = I-squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Ziprasidone

One RCT[96] (n = 306) compared chlorpromazine (100–1200 mg/d) with ziprasidone (40–160 mg/d) in **Asian patients** with chronic or subchronic **treatment-resistant schizophrenia** (Table 16). There were no reported results for **core illness symptoms**. There was no difference in **response rates** between groups (Table 17). No other relevant outcomes were reported.

Table 16. Characteristics of RCT comparing chlorpromazine versus ziprasidone in the treatment of schizophrenia and related psychoses.

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2006[96] RCT (12 wks)	G1: CHL (100–1200mg/d); (154) G2: ZIP (40–160mg/d); (152) Run-in phase: 6 wks	Chronic/ subchronic Sz; tx resistant; HAL nonresponders with no response to HAL during run-in phase	Unclear, Industry

AP(s) = antipsychotic(s); CHL = chlorpromazine; HAL = Haloperidol; G = group; Mg = milligrams; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); ZIP = ziprasidone

Table 17. Evidence summary table: chlorpromazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Response rates[96]	1	306	0.95 (0.78, 1.16)*	NE	ND

* = binary outcome; I^2 = I-squared; ND = no difference; NE = not estimable

Fluphenazine Versus Olanzapine

One RCT[89] (n = 60) compared fluphenazine (6–21 mg/d) with olanzapine (5–20 mg/d) in **Caucasian patients** with stable schizophrenia (Table 18). For **positive symptoms**, a significant difference favored olanzapine based on PANSS (positive) (Table 19). For **general psychopathology**, significant differences favoring olanzapine based on the Hamilton Rating Scale for Anxiety (HAM–A) and the PANSS (general psychopathology) were reported (Table 19). **Global Ratings** and **Total Scores** reported significant benefits favoring olanzapine for the BPRS, CGI–S, and PANSS (total) scales (Table 19). The results for the core illness symptoms were not considered to be clinically significant, and the SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 20). No significant differences were found for **negative symptoms** based on PANSS (negative) and **response rates** (Table 19).

Table 18. Characteristics of RCT comparing fluphenazine versus olanzapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Jakovljevic et al. 1999[89] RCT (22 wks)	G1: FLU (6–21mg/d); (30) G2: OLA (5–20mg/d); (30) Washout period: 1–1.5 wks	SZ; no unstable illness hx or intolerance to OLA or FLU w/ depot AP; no previous trial with OLA	Unclear, Industry

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Hx = history; Mg = milligrams; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; W/ = with; Wks = weeks

Table 19. Evidence summary table: fluphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[89]	1	60	5.10 (0.57, 9.63)	NE	olanzapine
Negative Symptoms					
PANSS[89]	1	60	3.00 (-1.00, 7.00)	NE	ND
General Psychopathology					
HAM–A[89]	1	60	4.00 (0.28, 7.72)	NE	olanzapine
PANSS[89]	1	60	8.20 (0.83, 15.57)	NE	olanzapine
Global Ratings and Total Scores					
BPRS[89]	1	60	9.30 (0.57, 18.03)	NE	olanzapine
-CGI–S[89]	1	60	0.90 (0.17, 1.63)	NE	olanzapine
PANSS[89]	1	60	16.20 (1.22, 31.18)	NE	olanzapine
Other Outcomes					
Response rates[89]	1	60	0.74 (0.51, 1.07)*	NE	ND

Note: bolded outcomes are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 20. Strength of evidence (GRADE): fluphenazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
HAM–A	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Fluphenazine Versus Quetiapine

One RCT[67] (n = 25) compared fluphenazine (10–15 mg/d) versus quetiapine (300–500 mg/d) in patients with **treatment-resistant** schizophrenia (Table 21). No significant differences were reported between groups for **core illness symptoms** (global ratings), **sexual dysfunction**, and **response rates** (Table 22). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 23).

Table 21. Characteristics of RCT comparing fluphenazine versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 2005[67] RCT (12 wks)	G1: FLU (10–15mg/d); (13) G2: QUE (300–500mg/d); (12) Run-in phase: 4–6 wks	Tx resistant Sz; persistent positive psychotic symptoms; failed tx trials with 2 different APs	Unclear, Multiple sources

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Mg = milligrams; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = Treatment; Wk(s) = week(s)

Table 22. Evidence summary table: fluphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Global Ratings					
BPRS[67]	1	25	-1.98 (-12.96, 9.00)	NE	ND
CGI–S[67]	1	25	-0.03 (-0.92, 0.86)	NE	ND
Sexual Dysfunction					
Dysfunction[67]	1	25	2.15 (0.72, 6.48)*	NE	ND
Improvement on treatment[67]	1	25	0.46 (0.05, 4.46)*	NE	ND
Other Outcomes					
Response rates[67]	1	25	0.62 (0.12, 3.07)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable

Table 23. Strength of evidence (GRADE): fluphenazine versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Fluphenazine Versus Risperidone

One RCT[67] (n = 26) compared fluphenazine (10–15 mg/d) with risperidone (3–5 mg/d) in patients with **treatment-resistant** schizophrenia (Table 24). No differences were found between groups for any of the **core illness symptom** assessments (global ratings), **sexual dysfunction**, and **response rates** (Table 25). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 26).

Table 24. Characteristics of RCT comparing fluphenazine versus risperidone in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 2005[67] RCT (12 wks)	G1: FLU (10–15mg/d); (13) G2: RIS (3–5mg/d); (13) Run-in phase: 4–6 wks	Tx resistant Sz; persistent positive psychotic symptoms; failed tx trials with 2 different APs	Unclear, Multiple sources

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Mg = milligrams; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s)

Table 25. Evidence summary table: fluphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Globa Ratings					
BPRS[67]	1	26	-0.30 (-10.80, 10.20)	NE	ND
CGI–S[67]	1	26	0.07 (-0.77, 0.91)	NE	ND
Sexual dysfunction					
Sexual dysfunction[67]	1	26	1.40 (0.60, 3.28)*	NE	ND
Improvement on treatment[67]	1	26	0.17 (0.02, 1.20)*	NE	ND
Other outcomes					
Response rates[67]	1	26	0.67 (0.13, 3.35)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable

Table 26. Strength of evidence (GRADE): fluphenazine versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Haloperidol Versus Aripiprazole

Key Points

- Eight RCTs compared haloperidol with aripiprazole among patients with varying disease severity.
- Six studies assessing global ratings using three different tools (BPRS, CGI–I, and CGI–S) found no differences between study groups. The SoE was graded as low or insufficient depending on the scale used.
- A significant difference in favor of aripiprazole was found for negative symptoms based on three studies that used the PANSS (negative) scale (moderate SoE). This finding was not considered to be clinically significant.
- No difference was found for positive symptoms based on two studies that used the PANSS (positive) scale (low SoE).
- Five studies assessed response rates and showed no differences between groups.

- The remaining outcomes were assessed in single trials, and the majority showed no significant differences.

Eight RCTs[31,44,73,74,76,92,98,102] (n = 2,850) compared haloperidol with aripiprazole. Key characteristics of the included trials and summary of findings are presented in Table 27 and Table 28, respectively. Five trials[31,73,74,76,92] specifically included patients with schizoaffective disorder, whereas one trial[44] specifically excluded patients with schizoaffective disorder. Five studies[31,44,74,76,92] specifically excluded patients with drug and/or alcohol dependence. Two studies[98,102] included only patients with multiple episodes, whereas the remaining studies included patients with both first and multiple episodes. Five studies[31,44,73,74,98] included only patients with no treatment resistance; the remaining three studies included mixed populations with both treatment resistance and no treatment resistance. One trial[102] included only Asian patients. In the majority of studies, the maximum dose of haloperidol was 10 mg/d; in two studies the maximum dose was 15 mg/d[76] and 30 mg/d.[73] The dosage for aripiprazole varied across studies ranging from 1 mg/d[31] to 45 mg/d.[73]

Risk of bias was unclear for five studies[31,44,74,98,102] and high for three studies.[73,76,92] The duration of followup was <6 weeks in five studies,[31,44,73,74,92] between 6 weeks and 6 months in two studies,[76,102] and >6 months in one study.[98] Six studies[31,44,74,76,92,98] were funded by industry; in all cases the industry manufactured aripiprazole.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of trials (Table 29).

Table 27. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of schizophrenia and other related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Andrezina et al. 2006[44] RCT (24 hrs)	G1: HAL (6.5mg/ 2 hrs; max 3/d); (185) G2: ARI (9.75mg/ 2 hrs; max 3/d); (175)	Sz or schizoaffective with agitation and no use of benzodiazepines or anticholinergics ≤4 hr; lack of response to previous AP	Unclear, Industry
Daniel et al. 2007[74] RCT (5 d)	G1: HAL (6.5mg/d); (151) G2: ARI (9.75mg/d); (153)	Acutely agitated Sz or schizoaffective disorder	Unclear, Industry
de Oliveira et al. 2009[76] RCT (8 wks)	G1: HAL (10–15mg/d); (33) G2: ARI (15–30mg/d); (66)	Sz/ schizoaffective disorder	High, Industry
Kane et al. 2002[92] RCT (4 wks)	G1: HAL (10mg/d); (104) G2: ARI (15mg/d); (102) G3: ARI (30mg/d); (102) Washout period: <1 wks	Sz/ schizoaffective disorder not refractory to antipsychotics; improvement with AP besides CLO; OP >1 3–month period <1 yr	High, Industry
Kasper et al. 2003[98] RCT (52 wks)	G1: HAL (5–10mg/d); (433) G2: ARI (20–30mg/d); (861) Washout period: ≥5 d	Acute relapse of Sz; response to AP (except CLO); no hx tx resistance; ≥3 mo OP AP use in last yr; PANSS total ≥60	Unclear, Industry
Kim et al. 2010[102] RCT (8 wks)	G1: HAL (15.9±7.1mg/d); (35) G2: ARI (21.7±5.5 mg/d); (31) Washout period: >4wks	Sz not further defined	Unclear, Foundation

Table 27. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of schizophrenia and other related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
McCue et al. 2006[73] RCT (3 wks)	G1: HAL (4–30mg); (61) G2: ARI (10–45mg); (63)	Sz, schizoaffective disorder or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Tran-Johnson et al. 2007[31] RCT (24 hrs)	G1: HAL (7.5mg/d); (60) G2: ARI (1mg/d); (57) G3: ARI (5.25mg/d); (63) G4: ARI (9.75mg/d); (57) G5: ARI (15mg/d); (58)	Sz, schizoaffective, or schizophreniform disorder; acute agitation	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP = bipolar disorder; CLO = clozapine; D = day; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Max = maximum; Mg = milligram; OP = outpatient; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

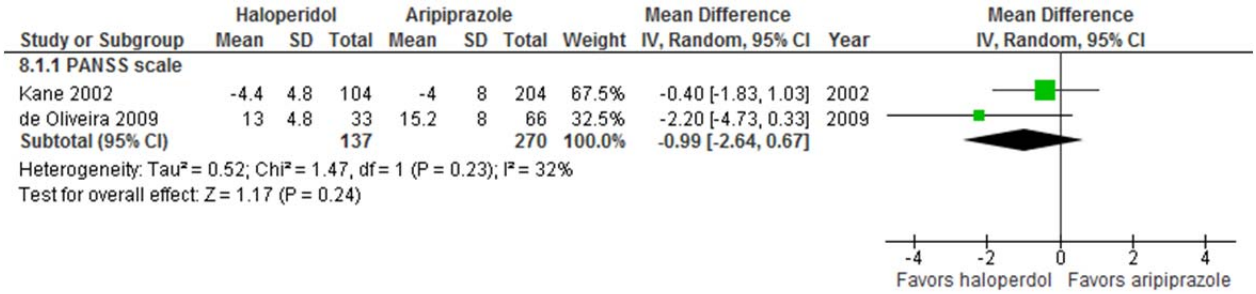
Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Three trials[76,92,102] (n = 473) assessed positive symptoms using two different scales. Two of the studies[76,92] included only patients with schizoaffective disorders and no alcohol and/or drug use; the third study[102] only included Asians and a mixed population in terms of disorder subtypes and comorbid drug or alcohol use. Studies were consistent in the dosages of study drugs. Duration of followup was <6 weeks for one study[92] and 8 weeks for two studies.[76,102] Risk of bias was high for two studies[76,92] and unclear for one study.[102] Two of the studies were industry-funded.[76,102]

No significant differences were found based on the PANSS (positive; two studies)[76,92] and Scale for the Assessment of Positive Symptoms (SAPS; 1 study)[102] (Table 28; Figure 4). There was moderate statistical heterogeneity between the two studies that reported PANSS scores; the only notable differences between these studies were duration of followup of 4 weeks[92] versus 8 weeks[76] and risk of bias (high[92] vs. unclear[76]). The SoE was graded as low for PANSS (positive) and insufficient for SAPS (Table 29).

Figure 4. Haloperidol versus aripiprazole – Positive symptoms



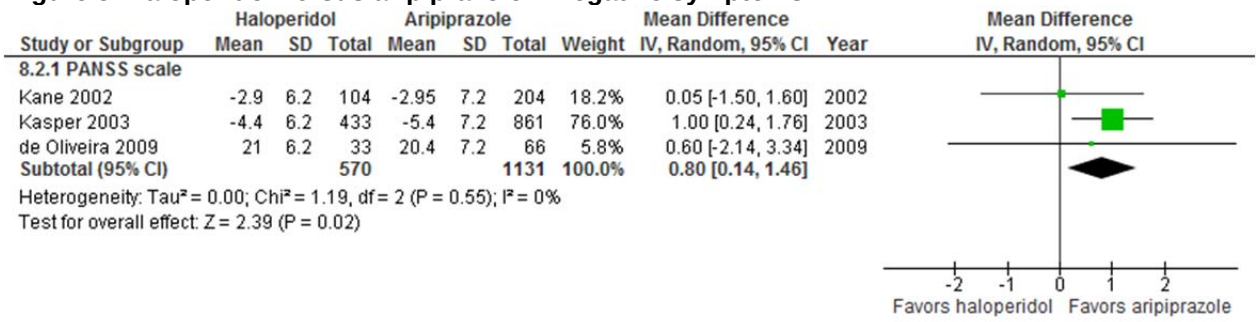
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Negative Symptoms. Four trials[76,92,98,102] (n = 1767) reported on negative symptoms. Two trials[76,92] specifically included patients with schizoaffective disorders and no comorbid drug or

alcohol use; two trials[98,102] included mixed populations in terms of disorder subtype and cormorbid drug or alcohol use. Two trials[98,102] included only patients with multiple episodes, whereas two trials[76,92] included mixed first and multiple episodes. One trial[98] specifically excluded treatment-resistant patients, and one study[102] included only Asians. One trial[102] included a higher range of haloperidol dose; the doses of aripiprazole were consistent across studies. Risk of bias was high for two studies[76,92] and unclear for two studies.[98,102] All studies were industry-funded except one.[102]

There was a significant difference favoring aripiprazole based on PANSS (negative), with no evidence of statistical heterogeneity (Table 28; Figure 5).[76,92,98] This difference was not considered to be clinically significant. There was no difference in the SANS[102] based on one small study (Table 28). The SoE was graded as moderate for PANSS (negative) and insufficient for SANS (Table 29).

Figure 5. Haloperidol versus aripiprazole – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

One trial comparing 7.5 mg/d haloperidol with 1 mg/d aripiprazole reported results for the Agitation-Calmness Evaluation Scale (ACES) and Corrigan Agitated Behavior Scale (CABS),[31] and showed no differences between study groups. The study specifically included patients with schizoaffective disorders and no comorbid alcohol or drug use. The study excluded patients with treatment resistance and included both first and multiple episodes. Length of followup was only 24 hours. Risk of bias was unclear, and the study was industry-funded.

One trial[76] (n = 99) reported PANSS (general psychopathology) and found no differences between groups over the 8-week study period (Table 28). The trial included only patients with schizoaffective disorders and no comorbid alcohol or drug use; the trial included a mix of first and multiple episodes, as well as treatment-resistant and nonresistant patients. Risk of bias was high, and the trial was industry-funded.

The SoE for PANSS (negative), ACES, and CABS was graded as insufficient (Table 29).

Global Ratings and Total Scores

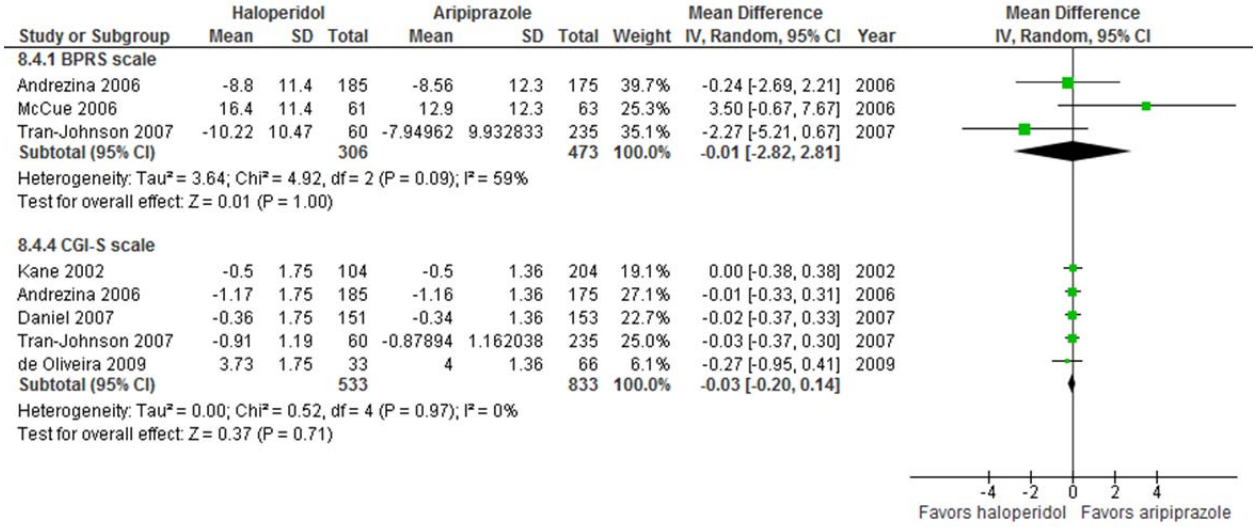
Six trials[31,44,73,74,76,92] (n = 1,490) presented global rating scores. No differences were found for BPRS (3 studies),[31,44,73] CGI–I (1 study),[31] or CGI–S (5 studies)[31,44,74,76,92] (Table 28; Figure 6). The SoE was graded as low for BPRS and CGI–S and insufficient for CGI–I (Table 29).

The three trials[31,44,73] that reported BPRS were statistically heterogeneous: one trial had an effect estimate favoring aripiprazole, and the other two favored haloperidol (although 95% CIs in all cases included the null). All three trials specifically included patients with schizoaffective

disorders and no treatment resistance, and included mixed first and multiple episodes. The one trial differed in that it did not specifically exclude patients with comorbid drug or alcohol use, and it used relatively higher doses of both haloperidol (4-30 mg/d vs. 6.5 and 7.5 mg/d) and aripiprazole (10-45 mg/d vs. 1 and 9.75 mg/d). Further, the duration of followup was longer for the one trial (3 weeks vs. 24 hours). The trial[73] that differed had high risk of bias and was not industry-funded, while the other two trials had an unclear risk of bias and were industry-funded.

The five trials[31,44,74,76,92] that reported CGI–S showed no evidence of statistical heterogeneity, but varied on several clinical and study characteristics. All studies specifically included patients with schizoaffective disorders except one[44] in which patients with schizoaffective disorders were excluded. Three studies[31,44,74] specifically excluded treatment-resistant patients, whereas two studies[76,92] had both treatment-resistant and nonresistant patients. All studies specifically excluded patients with comorbid drug or alcohol use. The range of dose for haloperidol was relatively consistent across studies; however, the dose for aripiprazole ranged from 1 mg/d[31] to 15–30 mg/d.[76,92] The duration of followup ranged from 24 hours[31,44] to 8 weeks.[76] Risk of bias was unclear for all but one trial, which was high;[92] all trials were industry-funded.

Figure 6. Haloperidol versus aripiprazole – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

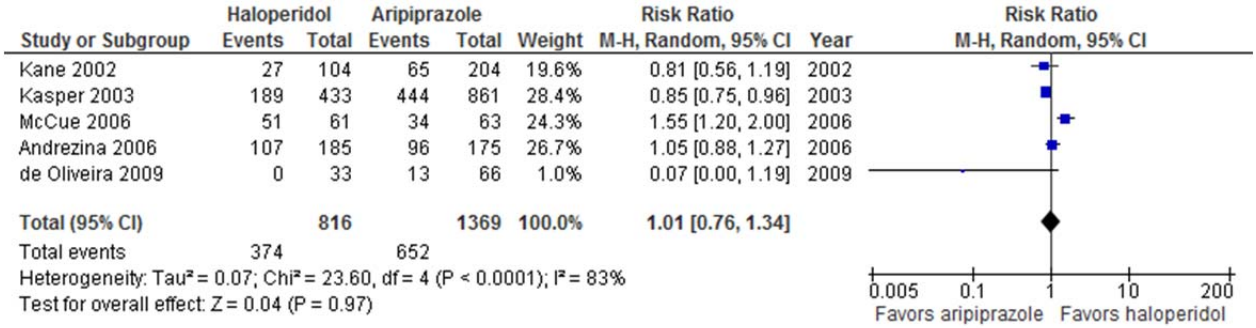
Other Outcomes

Five trials[44,73,76,92,98] (n = 2,185) assessed treatment response rates and found no significant difference between groups (Table 28; Figure 7); however, there was considerable statistical heterogeneity (Appendix M, Table 95). The trials varied on characteristics of the patient populations: schizoaffective disorder included,[73,76,92] schizoaffective disorder excluded,[44] mixed;[98] treatment-resistant patients excluded.[44,73,98] All but one trial[98] excluded patients with comorbid drug or alcohol use and included mixed first and multiple episodes. Doses ranged across studies from 6.5 to 4–30 mg/d for haloperidol and from 1 mg to 10–45 mg/d for aripiprazole. Duration of followup also varied across studies from 24 hours[44] to 52 weeks.[98] All

but one study[73] were assessed as unclear risk of bias and were industry-funded. None of these variables explained the statistical heterogeneity in the pooled estimate of effect.

One trial[76] (n = 99) comparing 10–15 mg/d haloperidol with 15–30 mg/d aripiprazole examined medication adherence, caregiver satisfaction, and patient satisfaction. The study reported a significant difference for caregiver and patient satisfaction favoring aripiprazole. There was no significant difference between groups for compliance rates (Table 28). This study specifically included patients with schizoaffective disorder, no comorbid drug or alcohol use, and mixed first and multiple episodes. Length of followup was 8 weeks. Risk of bias was unclear, and the study was industry-funded.

Figure 7. Haloperidol versus aripiprazole – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Key Question 5. Subgroups

Race

One trial[102] (n = 66) involving Korean patients with schizophrenia compared haloperidol (15.9±7.1 mg/d) with aripiprazole (21.7±5.5 mg/d) and reported no significant difference for positive (SAPS) or negative (SANS) core illness symptoms.

Table 28. Evidence summary table: haloperidol versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[76,92]	2	407	-0.99 (-2.64, 0.67)	32%	ND
SAPS[102]	1	66	-3.10 (-11.08, 4.88)	NE	ND
Negative Symptoms					
PANSS[76,92,98]	3	1701	0.80 (0.14, 1.46)	0%	aripiprazole
SANS[102]	1	66	-1.10 (-5.24, 3.04)	NE	ND
General Psychopathology					
ACES[31]	1	295	0.46 (-0.03, 0.95)	NE	ND
CABS[31]	1	295	-1.82 (-3.83, 0.18)	NE	ND
PANSS[76]	1	99	-1.60 (-5.28, 2.08)	NE	ND
Global Ratings					
BPRS[31,44,73]	3	779	-0.01 (-2.82, 2.81)	59%	ND
CGI–I[31]	1	295	-0.08 (-0.40, 0.25)	NE	ND
CGI–S[31,44,74,76,92]	5	1366	-0.03 (-0.20, 0.14)	0%	ND

Table 28. Evidence summary table: haloperidol versus aripiprazole (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Response rates[44,73,76,92,98]	5	2185	1.01 (0.76, 1.34)*	83%	ND
Low medication adherence[76]	1	99	0.66 (0.03, 15.70)*	NE	ND
Caregiver satisfaction[76]	1	99	0.32 (0.15, 0.67)*	NE	aripiprazole
Patient satisfaction[76]	1	99	0.33 (0.17, 0.66)*	NE	aripiprazole

Note: bolded results are statistically significant; * = binary outcome; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CGI–I = Clinical Global Impression–Intensity; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms

Table 29. Strength of evidence (GRADE): haloperidol versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	3 RCT	Medium	Consistent	Direct	Imprecise	Moderate (favoring aripiprazole)
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
ACES	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CABS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	5 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CGI–S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; ND = no difference

Haloperidol Versus Asenapine

One RCT[97] (n = 335) compared haloperidol (4 mg/d) with asenapine (5–10 mg/d) in patients with schizophrenia with acute exacerbation of psychotic symptoms (Table 30). This study did not find any significant differences between groups for **core illness symptoms** (positive, negative, or general psychopathology symptoms and global ratings and total scores) or for **response rates** (Table 31). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 32).

Table 30. Characteristics of RCTs comparing haloperidol versus asenapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2010[97] RCT (6 wks)	G1: HAL (4mg/d); (115) G2: ASE (5mg/d); (114) G3: ASE (10mg/d); (106) Washout period: 1–3 d	Sz with acute exacerbation of psychotic symptoms	Unclear, Industry

ASE = Asenapine; D = day; G = group; HAL = haloperidol; Mg = milligrams; RCT = randomized controlled trial; Sz = schizophrenia; Wk = week

Table 31. Evidence summary table: haloperidol versus asenapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[97]	1	335	0.16 (-1.22, 1.54)	NE	ND
Negative Symptoms					
PANSS[97]	1	335	0.39 (-0.72, 1.51)	NE	ND
General Psychopathology					
CDS–S[97]	1	335	0.56 (-0.20, 1.32)	NE	ND
PANSS[97]	1	335	0.26 (-1.59, 2.10)	NE	ND
Global Ratings and Total Scores					
CGI–S[97]	1	335	0.01 (-0.24, 0.25)	NE	ND
PANSS[97]	1	335	0.23 (-2.50, 2.95)	NE	ND
Other Outcomes					
Response rates[97]	1	335	0.82 (0.64, 1.04)*	NE	ND

* = binary outcome; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 32. Strength of evidence (GRADE): haloperidol versus asenapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
CDS–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CDS–S = Calgary Depression Scale for Schizophrenia; CGI–S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Haloperidol Versus Clozapine

Key Points

- Nine studies compared haloperidol with clozapine and involved patients with varying disease severity.
- Four studies assessed total scores using BPRS and three studies using PANSS. No differences were found between groups for either scale. Results were statistically heterogeneous for the PANSS total score, with one trial showing a significant difference favoring clozapine. This trial included patients with treatment-refractory schizophrenia and a history of high use of inpatient services; further, the study had a longer duration of followup (12 months vs. 12–14 weeks). The SoE was low for both BPRS and PANSS.
- The remaining outcomes were assessed in only one to two trials each; all showed no significant differences between study groups, except for CGI–I and CGI–S in a single study.

Nine RCTs[55,62,70,95,103,105,126,145,155] (n = 1,000) compared haloperidol with clozapine. Key characteristics of the included trials and summary of findings are presented in Table 33 and Table 34, respectively. All trials included various disorder subtypes, except for one study[103] that included only patients with paranoid schizophrenia; four studies[70,95,105,145] specifically included patients with schizoaffective disorders. Five trials[55,62,95,126,145] included patients with treatment-resistant schizophrenia, and one study[105] specifically excluded treatment-resistant patients. Five

trials[55,62,95,126,145] included only patients with multiple episodes. Two trials[55,95] specifically excluded patients with comorbid drug or alcohol use. The dosages varied across studies, ranging from 2.25 to 30 mg/d for haloperidol and 12.5 to 900 mg/d for clozapine.

Risk of bias was unclear for all but two studies,[62,95] which were high. Five studies were funded; by producers of clozapine,[62,95] both haloperidol and clozapine,[126,145] or makers of other antipsychotics.[105] Duration of followup varied: <6weeks for one study;[103] between 6 weeks and 6 months for five studies;[55,62,105,145,155] and >6 months for three studies.[70,95,126]

Publication bias was not formally tested for any of the outcomes due to the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient to low due to the small number of trials in individual outcomes assessments (Table 35).

Table 33. Characteristics of RCTs comparing haloperidol versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Breier et al. 1994[55] RCT (10 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–600mg/d); (38) Run-in phase: 6 wks	Chronic Sz not responding to 6 wks of FLU	Unclear, Government
Citrome et al. 2001[62] RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–800mg/d); (40) Run-in phase: 1 wk	Sz w/ suboptimal tx response; no depot AP <1 mo	High, Industry
Covington et al. 2000[70] RCT (24 mo)	G1: HAL (NR); (42) G2: CLO (NR); (40)	Sz or schizoaffective disorder	Unclear, Government
Itoh et al. 1977[155] RCT (12 wks)Kane et al. 2001[95] RCT (29 wks)	G1: HAL (5–16mg/d); (34) G2: CLO (12.5–800mg/d); (37)	Sz/ schizoaffective disorder, poor response (tx failure in >2 trials of conventional AP)	High, Industry
Klieser et al. 1994[103] RCT (4 wks)	G1: HAL (16mg/d); (17) G2: CLO (350mg/d); (17)	Acute paranoid Sz; no previous AP tx	Unclear, NR
Krakowski et al. 2006[105] RCT (12 wks)	G1: HAL (10–30mg/d); (36) G2: CLO (200–800mg/d); (37) Run-in phase: 1–2 wks	Schizophrenia or schizoaffective disorder; not hospitalized >1 yr or hx of nonresponse to CLO, OLA, or HAL	Unclear, Multiple sources including industry
Rosenheck et al. 1997[126] RCT (12 mo)	G1: HAL (5–30mg/d); (218) G2: CLO (10–900mg/d); (205)	Tx refractory Sz; hx of high level of use of inpatient services	Unclear, Multiple sources including industry
Volavka et al. 2002[145] RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–800mg/d); (40)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources

AP(s) = antipsychotic(s); CLO = clozapine; D = days; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; NR = not reported; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = year(s)

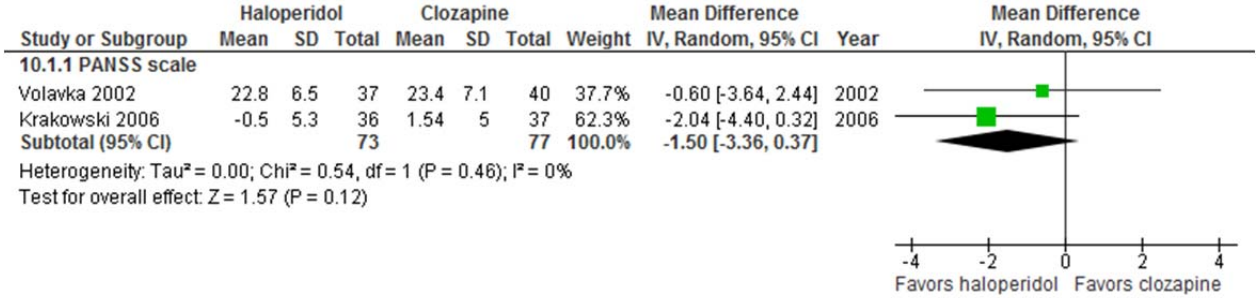
Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Two trials[105,145] (n = 150) assessed positive symptoms using PANSS (positive) and found no significant differences between groups (Table 34; Figure 8). The studies specifically included schizoaffective patients. One study[145] specifically included patients with multiple episodes with treatment resistance whereas the other study[105] excluded patients with treatment resistance. The doses of haloperidol (10–30 mg/d) and clozapine (200–800 mg/d) were consistent across studies.

Duration of followup was relatively consistent, ranging from 12 to 14 weeks. Risk of bias was unclear for both studies, and both were industry-funded. The SoE was low for PANSS (positive) (Table 35).

Figure 8. Haloperidol versus clozapine – Positive symptoms



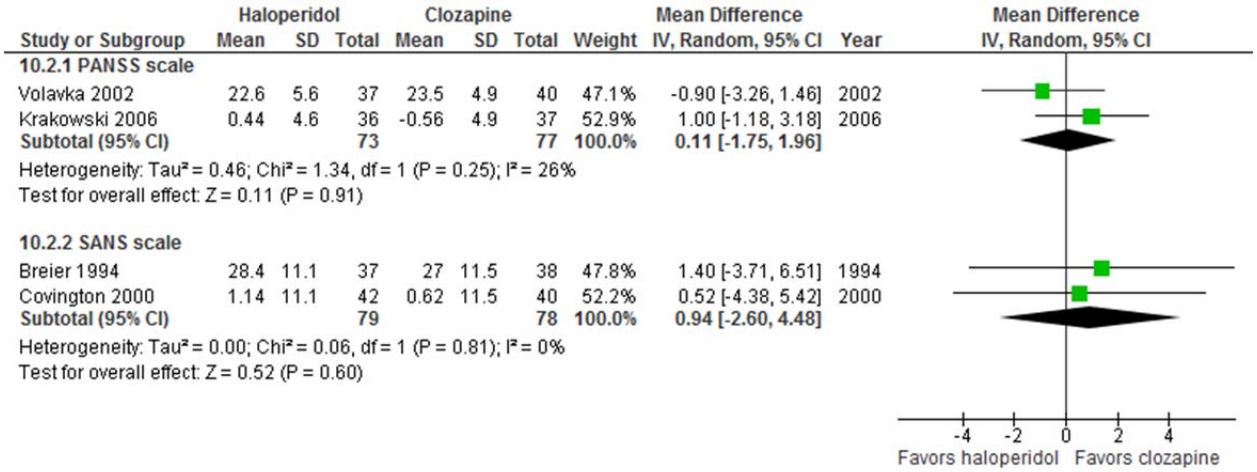
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Negative Symptoms

Four trials[55,70,105,145] (n = 307) compared haloperidol (10–30 mg/d) with clozapine (200–800 mg/d). Three[70,105,145] of the four trials specifically included patients with schizoaffective disorders. Two studies included only patients with multiple episodes,[55,145] whereas the other two trials included mixed first and multiple episodes. Two studies included only treatment-resistant patients assessed by history[145] and run-in;[55] one study[105] specifically excluded treatment-resistant patients. One trial[55] specifically excluded patients with comorbid drug or alcohol use. The drug doses were consistent in three studies, but not reported in one.[70] Duration of followup was 10 to 14 weeks for three studies and 24 months for the fourth.[70] Risk of bias was unclear for all studies; two studies were industry-funded[105,145] and two[55,70] were government-funded.

No significant differences between groups were found based on PANSS (negative)[55,70] and SANS[55,70] (Table 34; Figure 9). The SoE for both scales was graded as low (Table 35).

Figure 9. Haloperidol versus clozapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

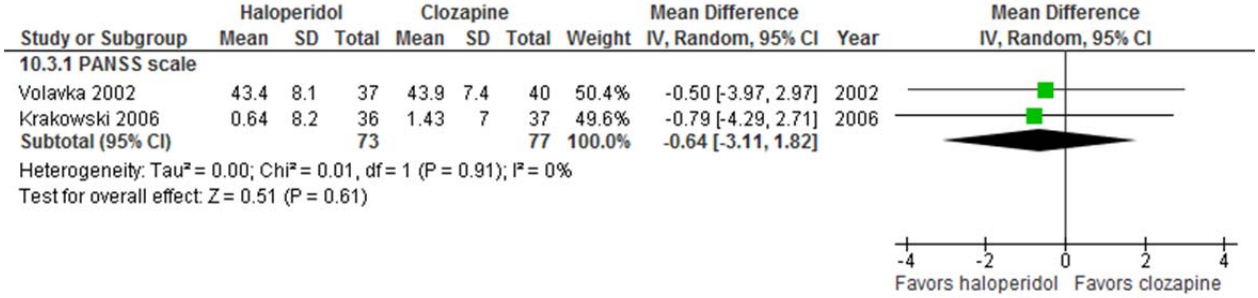
General Psychopathology

Two trials[105,145] (n = 150) used the PANSS (general psychopathology). Both trials specifically included patients with schizoaffective disorders. One trial[145] included only patients with multiple episodes, whereas the other study included patients with both first and multiple episodes. Treatment-resistant patients were included in one study[145] and excluded in the other. Both trials used the same doses of study drugs. Duration of followup was also consistent (12 and 14 weeks, respectively). Both studies had unclear risk of bias and were industry-funded.

The studies were consistent in their treatment estimates, and pooled results showed no significant difference between groups for general psychopathology (Table 34; Figure 10). The SoE was graded as low (Table 35).

One[105] of the above studies also reported results of the Modified Overt Aggression Scale (MOAS) and found no difference between groups (insufficient SoE).

Figure 10. Haloperidol versus clozapine – General psychopathology



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Score

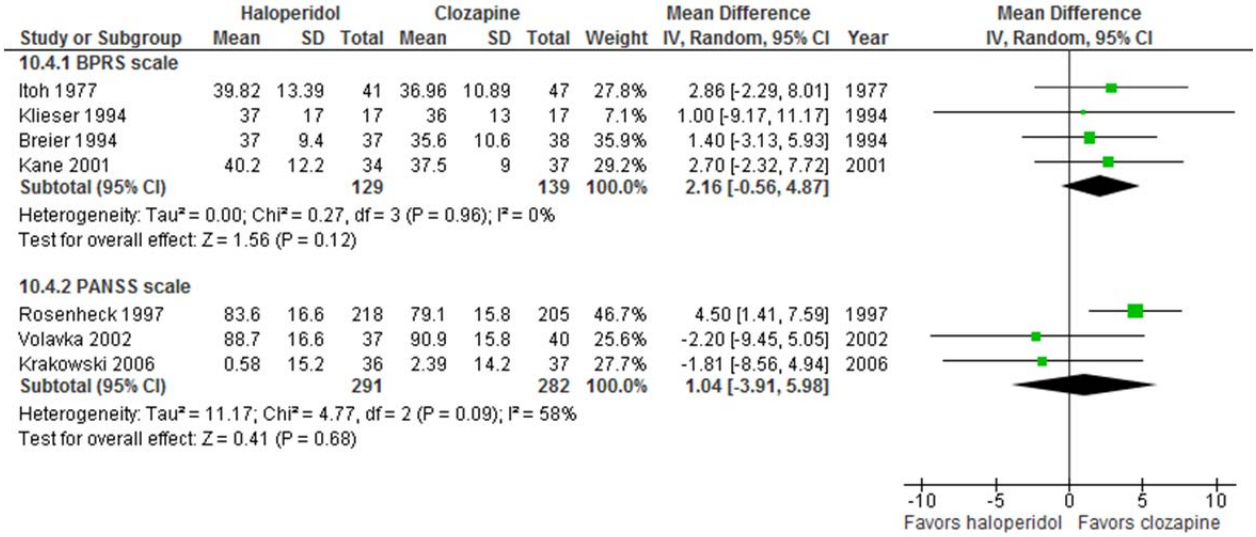
Seven trials[55,95,103,105,126,145,155] (n = 841) reported global ratings and total scores using four different scales. Four studies[55,95,103,155] used BPRS and reported consistent findings, with a pooled estimate showing no significant difference between groups (Table 34; Figure 11). These studies included varied disorder subtypes: paranoid schizophrenia,[103] schizoaffective disorders,[95] and mixed.[55,155] Two studies[55,95] included only patients with multiple episodes and treatment resistance and specifically excluded patients with comorbid alcohol or drug use. Duration of followup ranged from 4 weeks[103] to 29 weeks.[95] Risk of bias was unclear in all but one study,[95] which was high. Source of funding was not reported in two studies;[103,155] one study[95] was industry-funded and one was government-funded.[55]

Three studies used PANSS (total score).[105,126,145] The pooled estimate showed no significant difference between groups (Table 34; Figure 11); however, the statistical heterogeneity was substantial. Moreover, one of the studies[126] showed a significant difference in favor of clozapine, whereas the other two studies showed no significant difference. Removing this one study from the analysis reduced the heterogeneity to 0 percent, and the result remained nonstatistically significant. The trial differed from the other two with respect to several clinical and study characteristics. The two studies with similar estimates specifically included patients with schizoaffective disorders. The study that differed had a greater range of dosing: 5–30 mg/d versus 10–30 mg/d for haloperidol and 100–900 mg/d versus 200–800 mg/d for clozapine. Duration of followup differed substantially: 12 to 14 weeks for the two similar studies[105,145] versus 12 months.[126] All studies had unclear risk of bias and were funded by industry.

One study[95] assessed global rating scores using CGI–I and CGI–S (Table 34). The study included patients with schizoaffective disorder, multiple episodes, and treatment resistance. Patients with comorbid drug or alcohol use were specifically excluded. The doses were 5–16 mg/d for haloperidol and 12.5–800 mg/d for clozapine. Duration of followup was 29 weeks. The risk of bias was high, and the study was industry-funded. The results for both scales were statistically significant in favor of clozapine.

The SoE for BPRS and PANSS was graded as low; CGI–I and CGI–S were graded as insufficient (Table 35).

Figure 11. Haloperidol versus clozapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Health Care System Utilization

One trial[126] (n = 423) in patients with treatment-refractory schizophrenia compared haloperidol (5–30 mg/d) with clozapine (10–900 mg/d) and reported no significant differences in duration of hospital stay between groups (Table 34).

Other Outcomes

One trial examining treatment-resistant patients with mixed disorder subtypes, multiple episodes, and no cormorbid alcohol or drug use reported no significant difference in relapse rates (Table 34).[55] The study compared 5–16 mg/d haloperidol with 12.5–800 mg/d clozapine and followed patients for 29 weeks. Risk of bias was unclear, and the trial was government-funded.

Two studies assessed treatment response[95,105] and found no significant difference overall; however, there was substantial statistical heterogeneity. One study[95] showing a positive effect in favor of clozapine included patients with schizoaffective disorders, multiple episodes, treatment resistance, and no comorbid drug or alcohol use. The study compared 5–16 mg/d haloperidol with 12.5–800 mg/d clozapine. Duration of followup was 29 weeks. The study had high risk of bias and was industry-funded. This study also examined remission rates and found no significant

difference between groups. The second study[105] showed no significant difference between groups. It also included patients with schizoaffective disorders and multiple episodes; however, it included patients with both first and multiple episodes and excluded treatment-resistant patients. The risk of bias was unclear, and the trial was industry-funded.

Finally, one study[103] assessed patient satisfaction and found no significant difference between groups. The study included mixed disorder subtypes and patients with multiple episodes, treatment resistance, and no comorbid alcohol or drug use. The study compared 10–30 mg/d haloperidol with 200–600 mg/d clozapine and followed patients for 10 weeks. The risk of bias was unclear, and the study was government-funded.[103]

Key Question 5. Subgroups

Disorder Subtypes and Treatment Naïve

One trial[103] (n = 34) in treatment-naïve patients with paranoid schizophrenia compared 16 mg/d haloperidol with 12.5–800 mg/d clozapine and found no significant difference on BPRS.

Treatment Resistance

Five trials[55,62,95,126,145] (n = 88) in patients with treatment-refractory schizophrenia compared 5–30 mg/d haloperidol with 12.5–900 mg/d clozapine and found no significant differences for positive symptoms (PANSS (positive)[145]), negative symptoms (PANSS (negative),[145] SANS[55]), general psychopathology (PANSS (general psychopathology)[145]), or general ratings and total scores (BPRS,[55,95] PANSS (total)[126,145]). There were significant differences in favor of clozapine in one trial[95] for the general rating scale CGI–I (MD = 0.80; 95% CI, 0.26 to 1.34) and CGI–S (MD = 0.60; 95% CI, 0.13 to 1.07). This was not clinically significant.

Table 34. Evidence summary table: haloperidol versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[105,145]	2	147	-1.51 (-3.39, 0.37)	0%	ND
Negative Symptoms					
PANSS[105,145]	2	150	0.11 (-1.75, 1.96)	26%	ND
SANS[55,70]	2	157	0.94 (-2.60, 4.48)	0%	ND
General Psychopathology					
MOAS[105]	1	73	17.60 (-2.25, 37.45)	NE	ND
PANSS[105,145]	2	150	-0.64 (-3.11, 1.82)	0%	ND
Global Ratings and Total Scores					
BPRS[55,95,103,155]	4	268	2.16 (-0.56, 4.87)	0%	ND
CGI–I[95]	1	71	0.80 (0.26, 1.34)	NE	clozapine
CGI–S[95]	1	71	0.60 (0.13, 1.07)	NE	clozapine
PANSS[105,126,145]	3	573	1.04 (-3.91, 5.98)	58%	ND
Health Care System Utilization					
Mean hospital bed days[126]	1	423	-7.10 (-19.02, 4.82)	NE	ND
Other Outcomes					
Relapse rates[55]	1	75	0.68 (0.12, 3.87)*	NE	ND
Response rates[95,105]	2	144	0.64 (0.28, 1.47)*	72%	ND
Remission rates[95]	1	71	0.16 (0.02, 1.20)*	NE	ND
Patient satisfaction[103]	1	34	0.82 (0.46, 1.45)*	NE	ND

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; MOAS = Modified Overt Aggression Scale; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 35. Strength of evidence (GRADE): haloperidol versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SANS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
General Psychopathology						
MOAS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–I	1 RCT	Medium	Consistent	Direct	Precise	Insufficient
CGI–S	1 RCT	Medium	Consistent	Direct	Precise	Insufficient
PANSS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; MOAS = Modified Overt Aggression Scale; PANSS = Positive and Negative Symptom Scale; ND = No difference; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence

Haloperidol Versus Olanzapine

Key Points

- Twenty-nine studies compared haloperidol with olanzapine in patients with a range of illness severity.
- Sixteen studies reported positive symptoms using two different scales: PANSS (14 studies) and SAPS (2 studies). For both scales, the pooled results showed no differences between groups, and the SoE was low.
- Eighteen studies assessed negative symptoms using two scales: PANSS (14 studies) and SANS (5 studies). For both scales, results significantly favored olanzapine and in both cases the differences between groups were considered to be clinically important. The SoE was moderate for both scales.
- Eighteen studies reported general psychopathology using eight scales. Ten studies used the PANSS and found no differences between groups. Six studies used the Montgomery-Asberg Depression Rating Scale (MADRS) and found results significantly favored olanzapine, which was considered to be clinically relevant. Three studies used the Hamilton Rating Scale for Depression (HAM–D) and Calgary Depression Scale for Schizophrenia (CDS–S); only the HAM–D was found to significantly favor olanzapine. This difference was considered to be clinically significant. Two studies used the Agitated Behavior Scale (ABS), ACES, and HAM–A and found no differences. A single study used the Young Mania Rating Scale (YMRS) and showed no difference between groups. The SoE ranged from low to moderate.
- Twenty-two studies assessed global ratings and total scores using six scales: PANSS (15 studies), BPRS (13 studies), CGI–S (8 studies), CGI–I (2 studies), GAF (1 study), and Subjective Well-Being Under Neuroleptics scale (1 study). In all cases no significant differences were found except for the PANSS (total score), which showed a significant difference favoring olanzapine. This was considered to be clinically significant. Results for BPRS and CGI–S showed substantial statistical heterogeneity which may be partially explained by treatment resistance: when studies that included only patients with treatment resistance were removed from the analysis for BPRS, the results were homogeneous and

favored olanzapine. Removing one trial with first episode patients (not treatment resistant) from the analysis for CGI–S reduced the heterogeneity and results favored olanzapine. The SoE was moderate for PANSS and CGI–S, low for BPRS and CGI–I , and insufficient for the remaining scales.

- Response rates were assessed in 14 studies and showed a significant benefit for olanzapine. The statistical heterogeneity was substantial. As above, when studies that included only patients with treatment resistance were removed from the analysis, the results were homogeneous and favored olanzapine.
- Remission rates were assessed in three studies and showed a significant benefit for olanzapine.
- Five studies assessed health-related quality of life and showed no significant differences between groups.
- Other outcomes were assessed in single trials and showed no differences between groups.

Twenty-nine RCTs[43,49-51,54,56,58,71,73,75,78,88,91,101,102,104-106,108,110,124,127,129,130,136,141,145,147,159] (n = 5,750) compared haloperidol with olanzapine. Key characteristics of the included trials and summary of findings are presented in Table 36 and Table 37, respectively. One trial[43] included patients with paranoid schizophrenia, five studies[58,73,91,127,145] specifically included patients with schizoaffective disorder, and the remaining studies included mixed disorder subtypes. All studies included patients with both first and multiple episodes. Nine studies[51,58,73,78,105,110,130,141,145] included only patients with treatment resistance, which was ascertained from history in all cases. Three studies[91,124,129] specifically excluded patients with treatment resistance. Two studies[130,136] specifically included patients with comorbid alcohol or drug use, whereas nine studies[49-51,54,56,58,71,124,129] excluded patients with drug or alcohol use. Drug doses varied substantially across studies: from 1–4 mg/d[75] to 10–30 mg/d[58,105] for haloperidol and from 1–17.5mg/d[49] to 5–40 mg/d[73] for olanzapine. All studies included adults ranging in age from 18 to 64, except one study[78] that included only patients 17 to 28 years of age. Two studies[102,104] only included Asian patients.

Risk of bias was unclear for 19 studies[43,49-51,54,56,78,88,101,102,104-106,108,110,124,127,145,147] and high for 10 studies.[58,71,73,75,91,129,130,136,141,159] Duration of followup varied across studies: ≤6 weeks for 9 studies;[51,56,71,73,78,106,129,136,147] between 6 weeks and 6 months for 11 studies;[43,54,58,88,102,104,105,110,130,145,159] and ≥6 months for 9 studies.[49,50,75,91,101,108,124,127,141] Source of funding included: government (3 studies);[78,106,130] company that produces olanzapine (18 studies);[43,49-51,54,56,58,101,104,105,108,110,124,127,136,141,147,159] multiple companies, including producer of haloperidol (2 studies);[75,91] and multiple companies including producers of both drugs (1 studies).[145]

Publication bias was assessed for outcomes with at least 10 studies, and results are reported in the sections that follow. The SoE for the evaluated outcomes varied from insufficient to moderate mainly depending on the number of included trials and heterogeneity among the included trials (Table 38).

For each outcome, we examined whether differences existed for the various clinical characteristics (disorder subtypes, inclusion or exclusion of patients with schizoaffective disorder, sex, age group, race, comorbidities, previous exposure to antipsychotics, and treatment resistance), study characteristics (drug dose, followup period, and study sponsorship), and analytic methods (risk of bias and imputed data). When pooled estimates showed evidence of statistical heterogeneity, we report on any subgroups that had an effect on heterogeneity. All

other subgroups showed no effect. Appendix M (Tables 96–102) provides detailed tables on all subgroup analyses.

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Altamura et al. 2002[43] RCT (14 wks)	G1: HAL (10–20mg/d); (15) G2: OLA (10–20mg/d); (13) Washout period: 1 wk	Paranoid Sz with partial response to AP after ≥6 wks of different classes	Unclear, Industry
Avasthi et al. 2001[159] RCT (12 wks)	G1: HAL (5–20mg/d); (10) G2: OLA (5–20mg/d); (17)	Sz; CGI–S score >3	Unclear, Industry
Beasley et al. 1996[49] RCT (1 yr)	G1: HAL (10–20mg/d); (69) G2: OLA (2.5–7.5mg/d); (65) G3: OLA (7.5–12.5mg/d); (64) G4: OLA (12.5–17.5mg/d); (69) Washout period: variable depending on medication Run-in phase: <1 wk	Sz with acute exacerbation	Unclear, Industry
Beasley et al. 1997[50] RCT (1 yr)	G1: HAL (15±5mg/d); (81) G2: OLA (1.0mg/d); (88) G3: OLA (5±2.5mg/d); (87) G4: OLA (10±2.5mg/d); (86) G5: OLA (15±2.5mg/d); (89) Washout period: oral: >2 d; depot: >2 wks Run-in phase: 4–7 d	Sz with acute exacerbation	Unclear, Industry
Bernardo et al. 2001[51] RCT (4 wks)	G1: HAL (10mg/d); (13) G2: OLA (10mg/d); (14) Washout period: 1 wk	Sz/ schizophreniform disorder; no depot AP <6 mo	Unclear, Industry
Boulay et al. 2007[54] RCT (56 d)	G1: HAL (2.5–20mg/d); (11) G2: OLA (2.5–20mg/d); (14) Washout period: 3 d	Sz not further identified; no depot AP <6 mo	Unclear, Industry
Breier et al. 2002[56] RCT (24 hrs)	G1: HAL (7.5mg); (40) G2: OLA (2.5mg); (48) G3: OLA (5.0mg); (45) G4: OLA (7.5mg); (46) G5: OLA (10mg); (46) Washout period: 2–24 hrs	Hospitalized; Sz, schizophreniform disorder, schizoaffective disorder	Unclear, Industry
Buchanan et al. 2005[58] RCT (16 wks)	G1: HAL (10–30mg/d); (34) G2: OLA (10–30mg/d); (29) Run-in phase: 4 wks	Sz/ schizoaffective disorder with partial response to conventional APs, demonstrated >30% improvement on FLU, relapsed, or were intolerant of FLU during run-in phase	High, Multiple sources including industry
Crespo-Facorro et al. 2006[71] RCT (6 wks)	G1: HAL (3–9mg/d); (56) G2: OLA (5–20mg/d); (55) Washout period: 3–5 d	Sz with no AP <6 wks	High, Multiple sources
Davidson et al. 2009[75] RCT (6 mo)	G1: HAL (1–4mg/d); (103) G2: OLA (5–20mg/d); (105)	<2 yrs since onset of positive symptoms; <2 wks exposure to AP <1 yr; <6 wks lifetime exposure to AP	High, Industry
de Haan et al. 2003[78] RCT (6 wks)	G1: HAL (2.5mg/d); (12) G2: OLA (7.5mg/d); (12)	Sz; hx of unresponsiveness to HAL or OLA; no IM AP <1 yr	Unclear, Government
Ishigooka et al. 2001[88] RCT (8 wks)	G1: HAL (4–12mg/d); (89) G2: OLA (5–15mg/d); (93) Washout period: 2–4 wks	Sz; no tx with HAL, OLA or other investigational AP <3 mo; study AP contraindications	Unclear, NR

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Keefe et al. 2006[101] RCT (52 wks)	G1: HAL (2–19mg/d); (97) G2: OLA (5–20mg/d); (159)	Sz/ schizoaffective disorder; no previous AP ≤1 mo	Unclear, Industry
Kim et al. 2010[102] RCT (8 wks)	G1: HAL (15.9±7.1mg/d); (35) G2: OLA (15.9±4.3mg/d); (32) Washout period: >4wks	Sz not further defined	Unclear, Foundation
Kongsakon et al. 2006[104] RCT (24 wks)	G1: HAL (5–20 mg); (132) G2: OLA (5–20 mg); (144) Washout period: 2–9 d	Sz not further defined	Unclear, Industry
Krakowski et al. 2006[105] RCT (12 wks)	G1: HAL (10–30mg/d); (36) G2: OLA (10–35mg/d); (37) Run-in phase: 1–2 wks	Sz or schizoaffective disorder; not hospitalized >1 yr or hx of nonresponse to CLO, OLA, or HAL	Unclear, Multiple sources including industry
Lahti et al. 2009[106] RCT (6 wks)	G1: HAL (10–20mg/d); (14) G2: OLA (12.5–25mg/d); (18) Washout period: 2 wks	Sz defined by DSM–III–R	Unclear, Government
Lieberman et al. 2003[108] RCT (104 wks)	G1: HAL (2–20mg/d); (132) G2: OLA (5–20mg/d); (131) Washout period: <2 wks	Sz, schizophreniform, or schizoaffective disorder; onset <35 yrs; no AP drug tx >16 wks, previous CLO tx, or depot AP <3 dosing intervals	Unclear, Industry
Lindenmayer et al. 2007[110] RCT (12 wks)	G1: HAL (5–20mg/d); (19) G2: OLA (5–20mg/d); (16) Washout period: 1 wk cross-titration from previous AP	Sz defined by DSM–IV–TR	Unclear, Industry
McCue et al. 2006[73] RCT (3 wks)	G1: HAL (4–30mg); (61) G2: OLA (5–40 mg); (58)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Purdon et al. 2000[124] RCT (54 wks)	G1: HAL (5–20mg/d); (23) G2: OLA (5–20mg/d); (21) Washout period: 2–9 d Run-in phase: 1 mo	Sz <5 yrs of 1st exposure to AP; mild symptom severity	Unclear, Industry
Rosenheck et al. 2003[127] RCT (12 mo)	G1: HAL (5–20mg/d); (150) G2: OLA (5–20mg/d); (159)	Sz/ schizoaffective disorder; OP w/ hx of psychiatric hospitalization <2 yrs	Unclear, Industry
Saddichha et al. 2008[129] NRCT (6 wks)	G1: HAL (13.4±3.6mg/d); (31) G2: OLA (16.5±4.6mg/d); (35)	1st episode Sz; AP drug-naïve	High, NR
Sayers et al. 2005[130] RCT (26 wks)	G1: HAL (10–20mg/d); (12) G2: OLA (10–20mg/d); (12)	Sz and current cocaine abuse <6 mo; no depot AP <6 mo	High, Government
Smelson et al. 2006[136] RCT (6 wks)	G1: HAL (5–20mg/d); (15) G2: OLA (5–20mg/d); (16)	Sz; cocaine dependent; no DSM–IV criteria for other Axis I disorder	High, Industry
Tollefson et al. 1997[141] RCT (14 mo)	G1: HAL (5–20mg/d); (660) G2: OLA (5–20mg/d); (1336)	Sz; intolerant of current AP therapy (excluding HAL)	High, Industry

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Volavka et al. 2002[145] RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: OLA (10–40mg/d); (39)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources
Wright et al. 2001[147] RCT (24 hrs)	G1: HAL (7.5 mg); (126) G2: OLA (10 mg); (131)	Sz, schizophreniform disorder, or schizoaffective disorder	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar; CGI–S = Clinical Global Impression Severity Scale; CLO = clozapine; D = day; DSM–IV = Diagnostic and Statistical Manual of Mental Disorders – IV; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; IM = intramuscular; Mg = milligrams; Mo = month; NR = not reported; OLA = olanzapine; OP = outpatient; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Sixteen trials[50,51,54,71,88,101,102,104,105,108,110,124,136,141,145,159] (n = 3,920) reported no difference in positive symptoms using two scales (Table 37; Figure 12). The SoE for both scales was graded as low (Table 38).

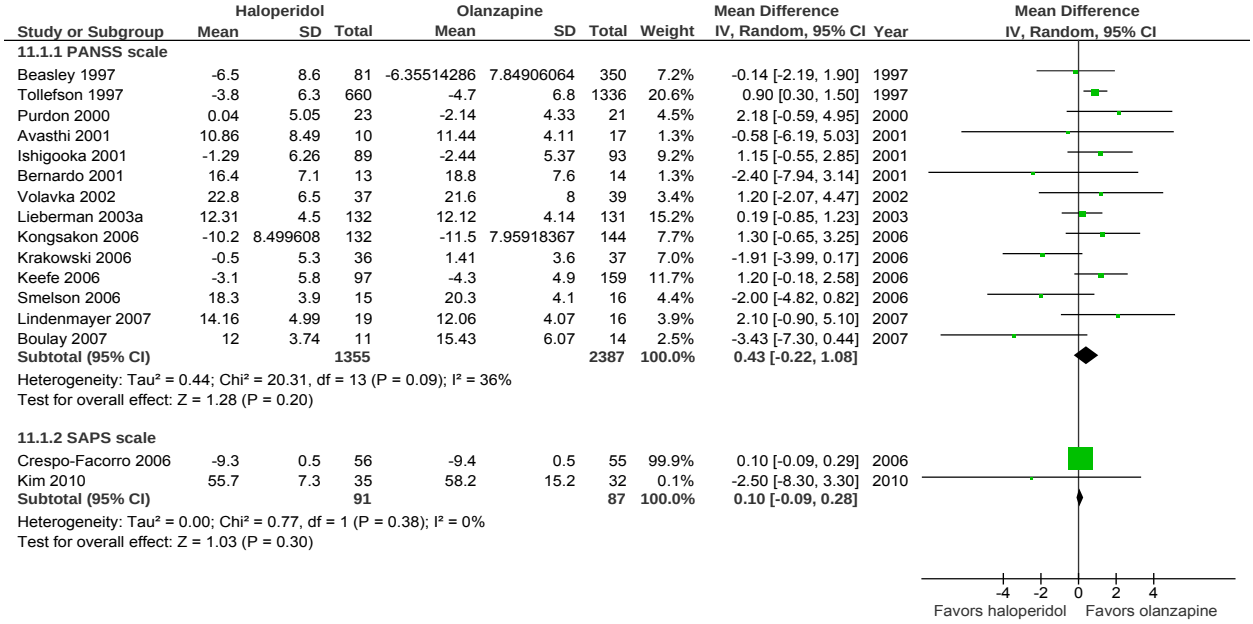
Fourteen trials[50,51,54,88,101,104,105,108,110,124,136,141,145,159] (n = 3,742) used PANSS (positive). Pooled results showed no significant difference between groups; however, there was moderate statistical heterogeneity (I^2 = 36 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: significantly favored olanzapine (I^2 = 17 percent);
- Olanzapine doses of ≤20 mg and haloperidol doses of ≤20 mg: significantly favored olanzapine (I^2 = 23 percent);
- Duration of followup >6 months: significantly favored olanzapine (I^2 = 0 percent);
- No imputed data: significantly favored olanzapine (I^2 = 17 percent).

The tests for publication bias were not significant, although the funnel plot appeared slightly asymmetrical, with studies showing larger effects for haloperidol (Appendix K, Funnel plot 1).

Two trials[71,102] (n = 178) showed no significant difference between groups based on SAPS. There was no evidence of statistical heterogeneity between the studies (I^2 = 0 percent).

Figure 12. Haloperidol versus olanzapine – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; SD = standard deviation

Negative Symptoms

Eighteen trials,[49-51,54,58,71,88,101,102,104,105,108,110,124,136,141,145,159] (n = 4,250) reported significant differences in favor of olanzapine on negative symptoms using two scales (Table 37; Figure 13). The SoE for these scales was graded as moderate (Table 38).

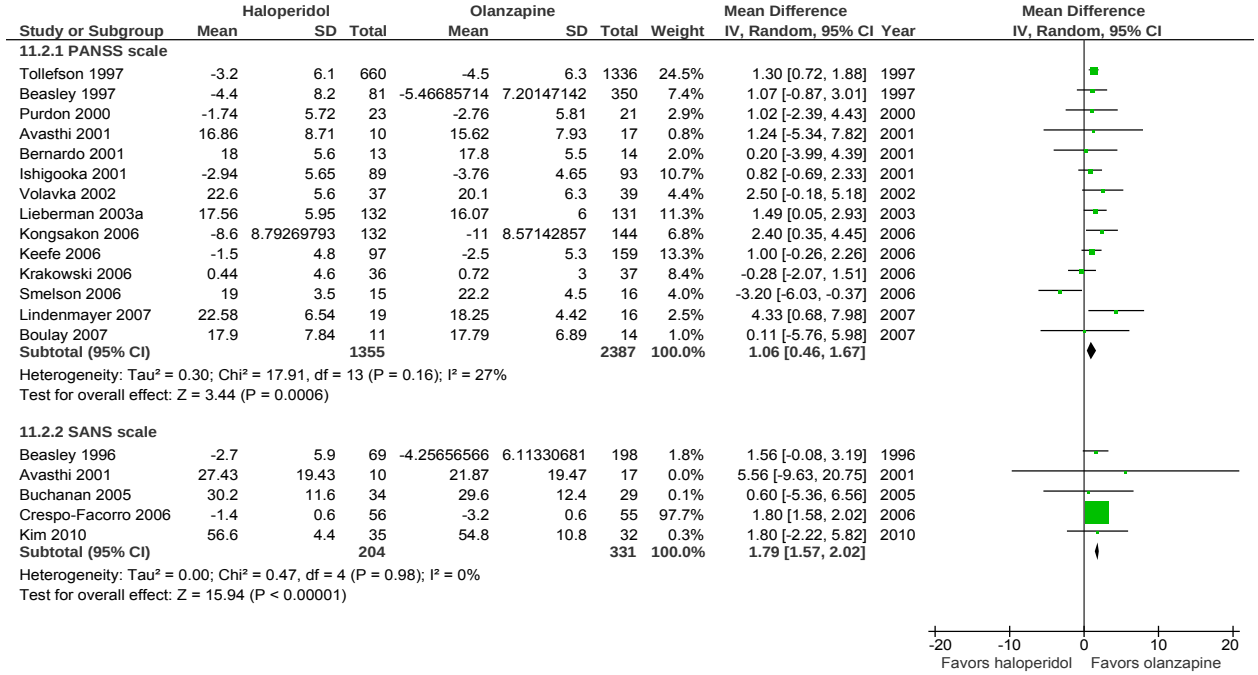
Fourteen studies (n = 3,742) used PANSS (negative).[50,51,54,88,101,104,105,108,110,124,136,141,145,159] Pooled estimates were significantly different between groups in favor of olanzapine, which was considered to be clinically significant. The results showed moderate statistical heterogeneity (I^2 = 27 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: significantly favored olanzapine (I^2 = 2 percent);
- Followup greater than 6 months (5 studies): significantly favored olanzapine (I^2 = 0 percent);
- Unclear risk of bias (11 studies): significantly favored olanzapine (I^2 = 0 percent).

There was no indication of publication bias based on statistical tests or visual examination of the funnel plot (Appendix K, Funnel plot 2).

Five trials[49,58,71,102,159] (n = 535) used SANS and reported significant results favoring olanzapine, which was considered to be clinically significant. There was no evidence of statistical heterogeneity across trials (I^2 = 0 percent).

Figure 13. Haloperidol versus olanzapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

General Psychopathology

Eighteen studies[50,54,56,58,71,78,88,91,101,105,108,110,124,136,141,145,147,159] (n = 4,327) assessed a range of other symptoms using eight scales (Table 37; Figure 14).

Ten trials[50,54,88,105,108,110,124,136,145,159] (n = 1,187) showed no difference based on PANSS (general psychopathology); however, the statistical heterogeneity was substantial (I^2 = 52 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: no difference between groups (I^2 = 25 percent);
- Studies that excluded cormorbid drug or alcohol use: no difference between groups (I^2 = 25 percent);
- Followup >6 months (4 studies): significantly favored olanzapine (I^2 = 0 percent);
- Unclear risk of bias (8 studies): no difference between groups (I^2 = 33).

There was no suggestion of publication bias based on statistical tests or visual inspection of the funnel plot (Appendix K, Funnel plot 3).

Three trials[58,71,110] (n = 209) used the HAM–D; the pooled results were significant in favor of olanzapine and showed no statistical heterogeneity (I^2 = 0 percent). This was considered to be clinically significant.

Six trials[78,101,105,108,141,159] (n = 2,639) used the MADRS. The pooled estimate showed significant results favoring olanzapine; there was no statistical heterogeneity across the studies (I^2 = 0 percent). This was considered to be clinically significant.

Three trials[54,71,91] (n = 344) reported CDS–S; the pooled result was not statistically significant, however the statistical heterogeneity was substantial (I^2 = 73 percent). One study[71] showed a significant benefit of olanzapine, whereas the other studies[54,91] showed no significant difference between groups. One study[91] specifically included schizoaffective disorder. Two

studies[54,71] excluded patients with comorbid drug or alcohol use. All studies included both treatment resistant and nonresistant patients. The dose of haloperidol varied across studies: 2.5–20 mg/d,[54] 3–9 mg/d,[71] and 1–4 mg/d.[91] The dose of olanzapine was more consistent with upper limits of 20 mg/d for all studies. Duration of followup varied from 6 weeks[71] to 1 year.[91] Risk of bias was high for two studies[71,91] and unclear for one.[54] Two trials[54,91] were industry-funded; the other[71] did not report a funding source.

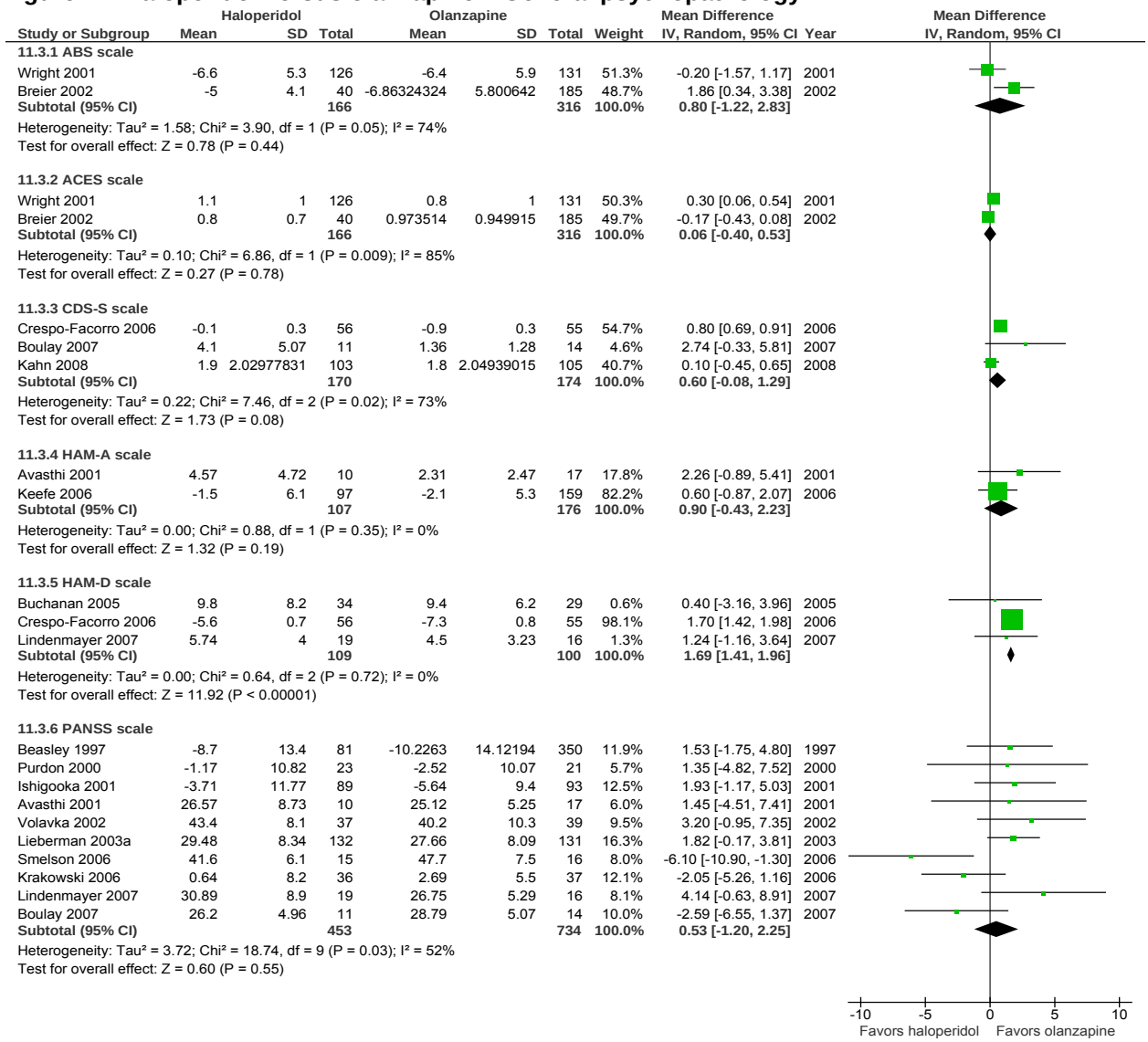
Two trials[101,159] (n = 283) showed no significant difference between groups based on the HAM–A (Table 37; Figure 14). There was no statistical heterogeneity across the studies ($I^2 = 0$ percent).

Two trials[56,147] (n = 482) found no significant difference based on the ABS and ACES. Statistical heterogeneity across studies was substantial ($I^2 = 74$ percent and 85 percent, respectively). Both studies included mixed populations in terms of disorder subtypes and treatment resistance. One study[56] specifically excluded patients with comorbid drug or alcohol use. Both studies used 7.5 mg/d of haloperidol and maximum 10 mg/d of olanzapine. Duration of followup was 24 hours for both studies. Both trials had unclear risk of bias and were funded by industry.

One study reported significant results favoring olanzapine based on the YMRS[71] (n = 111); these results were considered not to be clinically important.

The SoE was graded as moderate for the HAM–D and MADRS, whereas the HAM–A, PANSS (general psychopathology), ABS, ACES, and CDS–S were graded as low SoE. The SoE for YMRS was graded as insufficient (Table 38).

Figure 14. Haloperidol versus olanzapine – General psychopathology



ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; IV = inverse variance; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Scores

Twenty-two trials,[43,49-51,54,56,58,71,73,78,88,91,101,104-106,108,110,127,141,145,147] (n = 5,283) reported global ratings and total scores using six different scales (Table 37; Figure 15).

Fifteen trials[43,50,51,54,78,88,91,101,104,105,108,110,127,141,145] (n = 4,209) reported a statistically significant difference in favor of olanzapine based on PANSS (total). The difference was considered to be clinically important; however, there was moderate statistical heterogeneity (I^2 = 37 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Specifically included schizoaffective disorder (3 studies): no difference between groups (I^2 = 0 percent);

- Specifically excluded patients with comorbid drug or alcohol use (3 studies): no difference between groups ($I^2 = 0$ percent);
- Included both treatment resistant and nonresistant patients (8 studies): no difference between groups ($I^2 = 23$ percent);
- Followed patients for less than 6 weeks (2 studies): no difference between groups ($I^2 = 0$ percent);
- Followed patients for longer than 6 months (6 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Maximum doses of haloperidol and olanzapine of 20 mg/d (13 studies): significantly favored olanzapine ($I^2 = 23$ percent);
- No industry funding (2 studies): no difference between groups ($I^2 = 0$ percent);
- Imputed data for the meta-analysis (3 studies): no difference between groups ($I^2 = 0$ percent); no imputed data (12 studies): significantly favored olanzapine ($I^2 = 5$ percent).

There was no suggestion of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 4).

Thirteen trials[43,49-51,56,58,71,73,88,104,106,141,147] (n = 4,014) reported no significant difference between groups based on BPRS; however, the statistical heterogeneity was substantial ($I^2 = 82$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Included patients with and without comorbid alcohol or drug use (7 studies): significantly favored olanzapine ($I^2 = 36$ percent);
- Included treatment resistant and non-treatment-resistant patients (9 studies) (i.e., removed studies with only treatment resistant patients): significantly favored olanzapine ($I^2 = 0$ percent);
- Followed patients for >6 weeks and up to 6 months (4 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Did not report funding or had funding from sources other than industry (4 studies): significantly favored olanzapine ($I^2 = 0$ percent).

There was no suggestion of publication bias based on statistical tests (Appendix K, Funnel plot 5).

Eight trials[49,50,56,58,71,91,108,141] (n = 3,564) used the CGI–S, but pooled results are not presented due to substantial heterogeneity ($I^2 = 82$ percent) among the included trials. Restricting the analyses to the following subgroups reduced the heterogeneity:

- Patients with schizoaffective disorder (2 studies): no difference between groups ($I^2 = 34$ percent);
- Patients with and without comorbid drug or alcohol use (3 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Treatment-resistant patients (2 studies): significantly favored olanzapine ($I^2 = 32$ percent);
- Followed patients for >6 months (5 studies): significantly favored olanzapine ($I^2 = 7$ percent);
- Industry funding (7 studies): significantly favored olanzapine ($I^2 = 33$ percent);
- Unclear risk of bias (4 studies): no difference between groups ($I^2 = 11$ percent).

Further, one study appeared to be an outlier as it was the only study that significantly favored haloperidol. Removing this study reduced the heterogeneity to 33 percent and results

significantly favored olanzapine. This study included only patients with first episode and no treatment resistance.

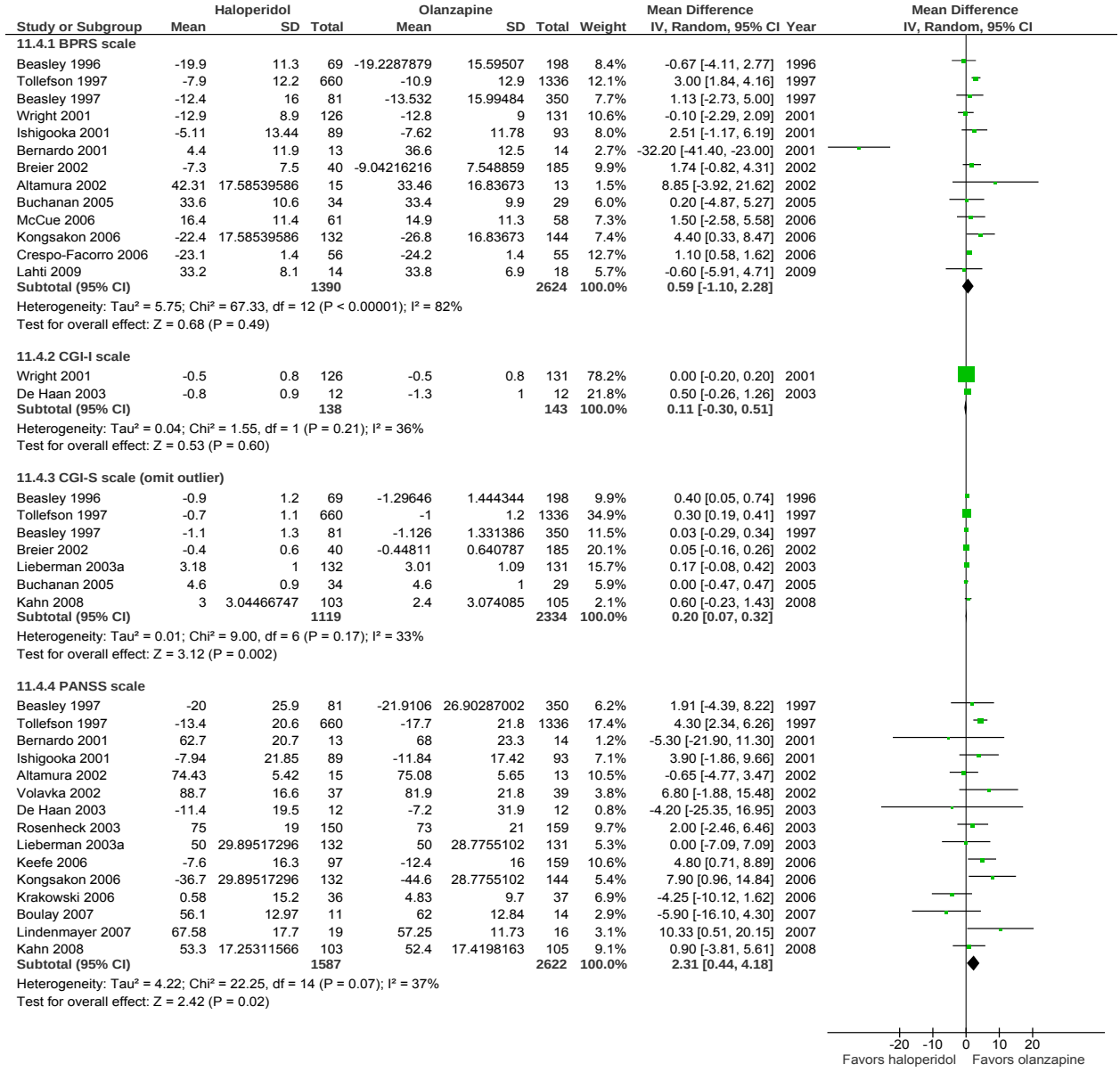
Two studies[78,147] used the CGI–I and pooled results showed no difference between groups. Statistical heterogeneity was moderate (I^2 = 36 percent). One study[78] specifically included patients with schizoaffective disorder, treatment resistant by history, and young adults (17–28 years). Both studies included patients with and without comorbid drug or alcohol use. One study[78] compared 2.5 mg/d haloperidol with 7.5 mg/d olanzapine, whereas the other study [147] examined doses of 7.5 mg/d and 10 mg/d, respectively. Duration of followup was 6 weeks[78] and 8 weeks. [147] Risk of bias was unclear for both studies; one was funded by government[78] and the other by industry. [147]

One study comparing 1–4 mg/d haloperidol with 5–20 mg/d olanzapine used the GAF and found no difference between groups.[91]

The Subjective Well–Being under Neuroleptics Scale was used in one study,[78] and no differences were found between groups.

The SoE for PANSS and CGI–S was graded as moderate; BPRS and CGI–I were graded as low; GAF and the Subjective Well-Being under Neuroleptics Scale were graded as insufficient (Table 38).

Figure 15. Haloperidol versus olanzapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; GAF = Global Assessment of Functioning; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Encounters With Legal System

One trial[136] (n = 31) that enrolled cocaine dependent patients compared 5–20 mg/d haloperidol with 5–20 mg/d olanzapine and found no difference between the groups for positive

urine cocaine toxicology (Table 37). Duration of followup was 6 weeks. Risk of bias was high and the trial was industry-funded.

Sexual Dysfunction

One trial[91] (n = 208) in patients with schizoaffective or schizophreniform disorder without treatment resistance compared 1–4 mg/d haloperidol with 5–20 mg/d olanzapine. The trial followed patients for one year and found no significant difference between groups regarding the incidence of sexual dysfunction (Table 37). The trial was considered high risk of bias and was industry-funded.

Health Care System Utilization

The same trial described above[91] found no significant difference between groups in terms of rates of hospitalization or rehospitalization (Table 37). One trial[127] found no difference in mean hospital bed days (Table 37).

Other Outcomes

Pooled results from 14 trials[49,71,73,88,91,101,104-106,108,110,130,141,147] (n = 4,099) showed a significant difference favoring olanzapine on response rates; however, statistical heterogeneity was substantial (I^2 = 55 percent) (Table 37; Figure 16). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mix of disorder subtypes (12 studies): significantly favored olanzapine (I^2 = 26 percent);
- Specifically excluded patients with comorbid drug or alcohol use (2 studies): no difference between groups (I^2 = 29 percent);
- Included treatment-resistant and nonresistant patients (8 studies): significantly favored olanzapine (I^2 = 0 percent);
- Followed patients for <6 weeks (4 studies): no difference between groups (I^2 = 0 percent);
- Followed patients for >6 weeks but <6 months (5 studies): no difference between groups (I^2 = 22 percent);
- No industry funding reported (5 studies): no difference between groups (I^2 = 0 percent);
- Unclear risk of bias (9 studies): significantly favored olanzapine (I^2 = 7 percent);
- Imputed data (3 studies): no difference between groups (I^2 = 0 percent).

There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 6).

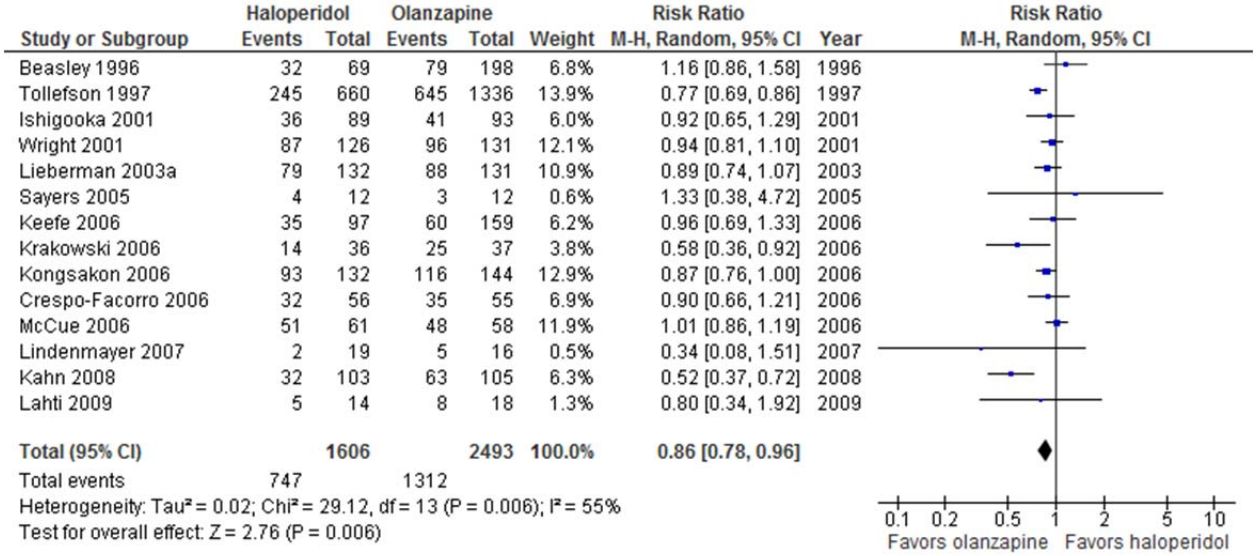
Three trials[71,91,108] (n = 582) assessed remission rates (Table 37). The pooled result was significant favoring olanzapine; however, there was substantial statistical heterogeneity. Removing one trial[91] from the analysis reduced the heterogeneity to 0 percent, and the result remained statistically significant. The trial differed from the other two in that it specifically included patients with schizoaffective disorder.

Single trials examined medication adherence[101] (n = 256) and patient insight into illness[108] (n = 263) and reported no differences between groups (Table 37). Characteristics of these studies are described in Table 36.

Five trials[49,58,91,104,159] examined health-related quality of life (HRQoL) using different scales; no differences were found between groups, and there was minimal statistical heterogeneity across the trials (Table 37). Two of the trials[58,91] specifically included patients with schizoaffective disorders. Two trials[49,58] specifically excluded patients with comorbid drug or alcohol use. One trial[104] included only patients of Asian descent. One study[58] used up to 30 mg/d

of both haloperidol and olanzapine and included only patients with treatment resistance. All studies followed patients for longer than 6 months. Risk of bias was unclear for two studies[49,104] and high for three;[58,91,159] all trials were industry-funded.

Figure 16. Haloperidol versus olanzapine – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Key Question 5. Subgroups

Age

One trial[78] (n = 24) in patients with schizophrenia aged 17–28 years found no differences between groups for general psychopathology (MADRS) or global ratings and total scores (CGI–I, PANSS (total), Subjective Well-Being under Neuroleptics Scale).

Comorbidities

Two trials[130,136] (n = 55) in patients with comorbid cocaine use reported no significant difference on the PANSS (positive), but a significant difference in favor of haloperidol on the PANSS (negative) (MD = -3.20; 95% CI, -6.03 to -0.37) and the PANSS (general psychopathology) (MD = -6.10; 95% CI, -10.90 to -1.30). The results for PANSS negative and general psychopathology were considered to be clinically significant.

Disease Subgroup

One trial[43] (n = 28) in patients with paranoid schizophrenia reported no significant difference on global ratings using the BPRS scale.

Race

Three trials,[88,102,104] (n = 525) in Asian patients reported no significant difference on PANSS (positive), SAPS, PANSS (negative), SANS, or PANSS (general psychopathology), but a significant difference in favor of olanzapine on BPRS (MD = 3.36; 95% CI, 0.63 to 6.09) and PANSS (total) (MD = 5.53; 95% CI, 1.10 to 9.96). The difference on BPRS and PANSS (total) were considered to be clinically significant.

Treatment of a First Episode

Four trials[71,75,108,129] (n = 928) included patients undergoing treatment for their first schizophrenic episode. There was no significant difference on PANSS (positive), SAPS, PANSS (general psychopathology), and CDS–S. However, there was a significant difference in favor of olanzapine on the YMRS (MD = 0.40; 95% CI, 0.21 to 0.59), PANSS (negative) (MD = 1.49; 95% CI, 0.05 to 2.93), SANS (MD = 1.80; 95% CI, 1.58 to 2.02), HAM–D (MD = 1.70; 95% CI, 1.42 to 1.98), and BPRS (MD = 1.10; 95% CI, 0.58 to 1.62). There was a significant difference favoring haloperidol on the CGI–S scale (MD = 0.80; 95% CI, 0.69 to 0.91).

Treatment Resistance

Nine trials[51,58,73,78,105,110,130,141,145] (n = 2,804) in treatment-resistant patients reported no difference in positive symptoms (PANSS [positive]),[51,105,110,141,145] negative symptoms (SANS),[58] general psychopathology (HAM–D,[58] PANSS (general psychopathology),[105,110,145] or global ratings and total scores (BPRS,[51,58,73,141] CGI–I,[78] PANSS,[51,78,105,110,141,145] and Subjective Well-Being under Neuroleptics Scale).[78] There was a significant difference favoring olanzapine for two scales: one measure general psychopathology (MADRS)[78,105,141] and the other a global rating scale (CGI–S).[58,141]

Table 37. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[50,51,54,88,101,104,105,108,110,124,136,141,145,159]	14	3742	0.43 (-0.22, 1.08)	36%	ND
SAPS[71,102]	2	178	0.10 (-0.09, 0.28)	0%	ND
Negative Symptoms					
PANSS[50,51,54,88,101,104,105,108,110,124,136,141,145,159]	14	3742	1.06 (0.46, 1.67)	27%	olanzapine
SANS[49,58,71,102,159]	5	535	1.79 (1.57, 2.02)	0%	olanzapine
General Psychopathology					
ABS[56,147]	2	482	0.80 (-1.22, 2.83)	74%	ND
ACES[56,147]	2	482	0.06 (-0.40, 0.53)	85%	ND
CDS–S[54,71,91]	3	344	0.60 (-0.08, 1.29)	73%	ND
HAM–A[101,159]	2	283	0.90 (-0.43, 2.23)	0%	ND
HAM–D[58,71,110]	3	209	1.69 (1.41, 1.96)	0%	olanzapine
MADRS[78,101,105,108,141,159]	6	2639	2.46 (1.78, 3.14)	0%	olanzapine
PANSS[50,54,88,105,108,110,124,136,145,159]	10	1187	0.53 (-1.20, 2.25)	52%	ND
YMRS[71]	1	111	0.40 (0.21, 0.59)	NE	olanzapine
Global Ratings and Total Scores					
BPRS[43,49-51,56,58,71,73,88,104,106,141,147]	13	4014	0.59 (-1.10, 2.28)	82%	ND
CGI–I[78,147]	2	281	0.11 (-0.30, 0.51)	36%	ND
CGI–S,[49,50,56,58,91,108,141] omit outlier	7	3453	0.20 (0.07, 0.32)	33%	olanzapine
GAF[91]	1	208	-4.00 (-13.70, 5.70)	NE	ND
PANSS[43,50,51,54,78,88,91,101,104,105,108,110,127,141,145]	15	4209	2.31 (0.44, 4.18)	37%	olanzapine
Subjective Well-Being under Neuroleptics Scale[78]	1	24	7.00 (-3.55, 17.55)	NE	ND
Encounters With the Legal System					
Positive urine toxicology[136]	1	31	3.20 (0.76, 13.46)*	NE	ND
Sexual dysfunction					
Sexual dysfunction (UKU)[91]	1	208	0.80 (0.52, 1.24)	NE	ND

Table 37. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[91]	1	208	0.79 (0.42, 1.51)*	NE	ND
Mean hospital bed days[127]	1	309	-7.10 (-20.95, 6.75)	NE	ND
Other Outcomes					
Response rates[49,71,73,88,91,101,104-106,108,110,130,141,147]	14	4099	0.86 (0.78, 0.96)*	55%	olanzapine
Remission rates[71,91,108]	3	582	0.65 (0.45, 0.94)*	54%	olanzapine
Medication adherence[101]	1	256	1.00 (0.81, 1.22)*	NE	ND
Patient insight into illness[108]	1	263	-1.10 (-3.95, 1.75)	NE	ND
Health-Related Quality of Life					
Health-related quality of life[159]	1	27	-2.05 (-25.81, 21.71)	NE	ND
MANSA[91]	1	208	0.00 (-1.38, 1.38)	NE	ND
QLS[49,58]	2	330	-2.62 (-6.39, 1.15)	0%	ND
Schizophrenia-specific QLS[104]	1	276	-3.62 (-8.94, 1.70)	NE	ND

Note: bolded results are statistically significant; * = binary outcome; ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; MADRS = Montgomery-Asberg Depression Rating Scale; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; NR = not reported; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; YMRS = Young Mania Rating Scale

Table 38. Strength of evidence (GRADE): haloperidol versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	14 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	14 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
SANS	5 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
General Psychopathology						
ABS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
ACES	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CDS–S	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM–A	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM–D	3 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
MADRS	6 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
PANSS	10 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
YMRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

Table 38. Strength of evidence (GRADE): haloperidol versus olanzapine (continued)

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Outcome						
BPRS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–I	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–S, omit outliers	7 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	15 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
SWBUN	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; ND = no difference; OLA = olanzapine; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; SWBUNS = Subjective Well-being Under Neuroleptics Scale; YMRS = Young Mania Rating Scale

Haloperidol Versus Quetiapine

Key Points:

- Nine studies compared haloperidol versus quetiapine in patients with a range of disease severity.
- Positive symptoms assessed using PANSS (4 trials) was not significantly different between groups (low SoE).
- Negative symptoms assessed using PANSS (4 trials) and SANS (1 trial) were not significantly different between groups. The results for PANSS were statistically heterogeneous with one of the trials (which was high risk of bias vs. unclear for the other three) showing a significant difference in favor of quetiapine. The SoE was low for PANSS and insufficient for SANS.
- General psychopathology was assessed using PANSS (general psychopathology) (4 trials), CDS–S (2 trials), and Beck Depression Inventory (BDI) (1 trial), and was not significantly different between groups. The SoE was low for PANSS and CDS–S and insufficient for BDI.
- Global ratings and total scores were assessed using PANSS (total) (6 trials), CGI–S (4 trials), BPRS (4 trials), CGI–I (3 trials), and GAF (1 trial). No differences were found for any scales except for CGI–S, which showed a significant benefit for haloperidol, which was not considered to be clinically significant. The SoE was low or insufficient for all scales except for CGI–S, which was moderate.
- Response rates were assessed in six studies and showed no difference between groups overall. One study was an outlier and showed a significant difference favoring haloperidol. This study of treatment-resistant patients used relatively higher doses of haloperidol (4–30 mg/d) and quetiapine (50–1200 mg/d) and followed patients for only 3 weeks.
- Other outcomes were assessed in a single trial and showed no differences between groups.

Nine RCTs,[46,47,65,68,73,79,80,91,123] (n = 1,516) compared haloperidol (1–200 mg/d) with quetiapine (50–1200 mg/d). Key characteristics of the included trials and summary of findings are presented in Table 39 and Table 40. All studies included mixed populations in terms of first versus repeat episodes. One study[80] specifically included patients with schizoaffective disorder, whereas the others included mixed populations in terms of disorder subtypes. Three studies[47,73,123] specifically excluded patients with comorbid drug or alcohol use; the others included patients with and without comorbid drug or alcohol use. Two studies[73,79] included only treatment-resistant patients based on history; the other studies included mixed populations with respect to treatment resistance. One study[47] included only female patients, whereas the others included mixed male and female populations. The doses for haloperidol ranged from 1–4 mg/d[91] to 4–30 mg/d.[73] Likewise the doses for quetiapine varied with maximum doses ranging from 500 mg/d[65] to 1200 mg/d.[73]

Duration of followup was ≤6 weeks for four studies,[46,47,68,73] between four weeks and 6 months for two studies,[65,79] and ≥6 months for three studies.[80,91,123] Risk of bias was unclear in five studies[46,47,79,80,123] and high in four.[65,68,73,91] All studies reported having industry support except for two[47,73] that did not report their source of funding.

Publication bias was not formally tested for any of the outcomes due to the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient or low, largely due to the small number of trials (Table 41).

Table 39. Characteristics of RCTs comparing haloperidol versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Arvanitis et al. 1997[46] RCT (6 wks)	G1: HAL (12mg/d); (52) G2: QUE (75mg/d); (53) G3: QUE (150mg/d); (48) G4: QUE (300mg/d); (52) G5: QUE (600mg/d); (51) G6: QUE (750mg/d); (54) Washout period: 1 wk	Sz (chronic or subchronic) with no use of depot AP within one dosing interval	Unclear, Industry
Atmaca et al. 2002[47] RCT (6 wks)	G1: HAL (10mg/d); (17) G2: QUE (600mg/d); (18) Washout period: 2 wks	Sz defined by DSM–IV	Unclear, NR
Copolov et al. 2000[68] RCT (6 wks)	G1: HAL (1–16mg/d); (227) G2: QUE (50–800mg/d); (221) Washout period: 48 hrs	Acute exacerbation of chronic or subchronic Sz; no tx with a depot AP <1 dosing period	High, Industry
Emsley et al. 2000[79] RCT (12 wks)	G1: HAL (5–20mg/d); (145) G2: QUE (600mg/d); (143) Run-in phase: 4 wks	Sz; hx of partial response to conventional APs; persistent positive symptoms while previously taking AP; partial or no response to 1 mo FLU tx	Unclear, Industry
Emsley et al. 2005[80] RCT (2 yrs)	G1: HAL (5–20mg); (23) G2: QUE (100–800mg); (22)	Clinically stable Sz or schizoaffective disorder (DSM–IV); on stable dose of AP; had TD	Unclear, Multiple sources including industry
Glick et al. 2005[65] RCT (48 wks)	G1: HAL (200mg/wk); (14) G2: QUE (500mg/d); (21)	Sz requiring long-term therapy	High, Multiple sources including industry

Table 39. Characteristics of RCTs comparing haloperidol versus quetiapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kahn et al. 2008[91] RCT (12 mo)	G1: HAL (1–4mg/d); (103) G2: QUE (200–750mg/d); (104)	Sz/ schizophreniform or schizoaffective disorder; <2 yrs since onset of positive symptoms; no AP > 2 wks in last 1 yr, or >6 wks at any time	High, Industry
McCue et al. 2006[73] RCT (3 wks)	G1: HAL (4–30mg); (61) G2: QUE (50–1200 mg); (62)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Purdon et al. 2001[123] RCT (6 mo)	G1: HAL (10–20mg/d); (12) G2: QUE (300–600mg/d); (13) Washout period: 48 hrs	Sz defined by DSM–IV	Unclear, Industry

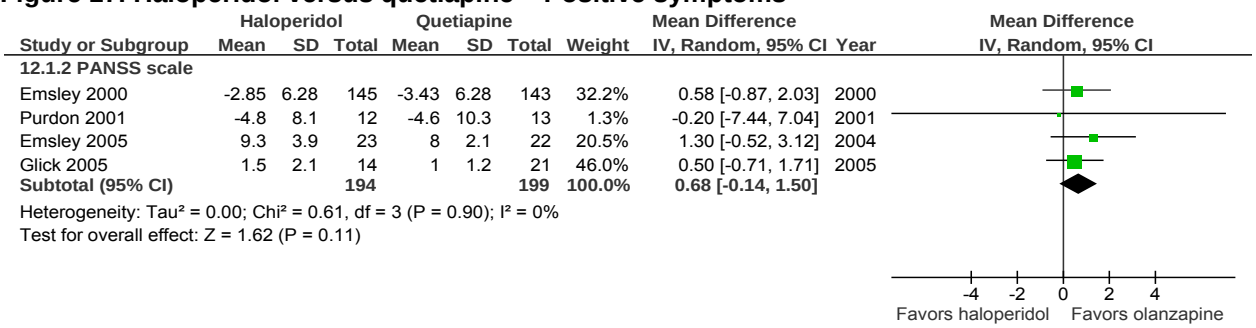
AP(s) = antipsychotic(s); BP = bipolar disorder; D = day; DSM–IV = Diagnostic and Statistical Manual of Mental Disorders – IV; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; NR = not reported; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; TD = tardive dyskinesia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Four trials[65,79,80,123] (n = 393) reported on positive symptoms using the PANSS (positive), and pooled results showed no significant difference between groups (Table 40; Figure 17); the trials were statistically homogenous. One of the studies[80] specifically included patients with schizoaffective disorder and treatment resistance based on history, whereas the others included mixed populations in terms of disorder subtypes and treatment resistance. One study[123] specifically excluded patients with comorbid drug or alcohol use. The dose of haloperidol was relatively consistent across studies except one[65] that gave 200 mg/wk. The dose of quetiapine ranged from 100–800 mg/d. Duration of followup was <6 months for two studies[65,79] and ≥6 months for two studies.[80,123] Risk of bias was high for one study[65] and unclear for the other three; all studies were industry-funded. The SoE for PANSS (positive) was graded as low (Table 41).

Figure 17. Haloperidol versus quetiapine – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

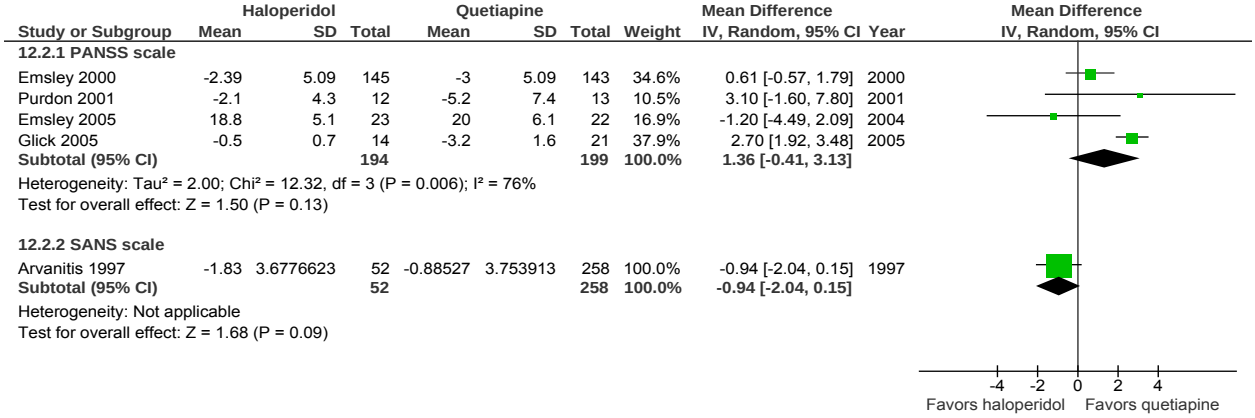
Negative Symptoms

Five trials,[46,65,79,80,123] (n = 703) reported negative symptoms using two scales (Table 40; Figure 18). Four trials,[65,79,80,123] (n = 393) reported no significant difference between groups using PANSS (negative); however, there was substantial statistical heterogeneity. We examined predefined subgroup and sensitivity analyses to explain the heterogeneity (Appendix M, Table 103). There was no change in heterogeneity based on disorder subtype, comorbid drug or alcohol use, treatment resistance, or duration of followup. Three studies had unclear risk of bias and had minimal statistical heterogeneity (I^2 = 10 percent); the pooled estimate showed no difference between groups. One study[65] with high risk of bias showed an important significant difference favoring quetiapine.

One trial[46] (n = 310) compared 12 mg/d haloperidol with 75–750 mg/d quetiapine and found no significant difference between groups using SANS (Table 40; Figure 18). This trial included mixed populations in terms of disorder subtypes, comorbid drug or alcohol use, and treatment resistance. Duration of followup was 6 weeks. Risk of bias was unclear, and the trial was industry-funded.

The SoE was low for PANSS (negative) and insufficient for SANS (Table 41).

Figure 18. Haloperidol versus quetiapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

Four trials[65,79,80,123] (n = 393) reported no significant difference between groups using PANSS (general psychopathology) (Table 40; Figure 19); there was minimal statistical heterogeneity across the studies. One of the studies[80] specifically included patients with schizoaffective disorder and treatment resistance based on history, whereas the others included mixed populations in terms of disorder subtypes and treatment resistance. One study[123] specifically excluded patients with comorbid drug or alcohol use. The dose of haloperidol was relatively consistent across studies except one[65] that gave 200 mg/d. The dose of quetiapine ranged from 100–800 mg/d. Duration of followup was <6 months for two studies[65,79] and ≥6 months for two studies.[80,123] Risk of bias was high for one study[65] and unclear for the other three; all studies were industry-funded.

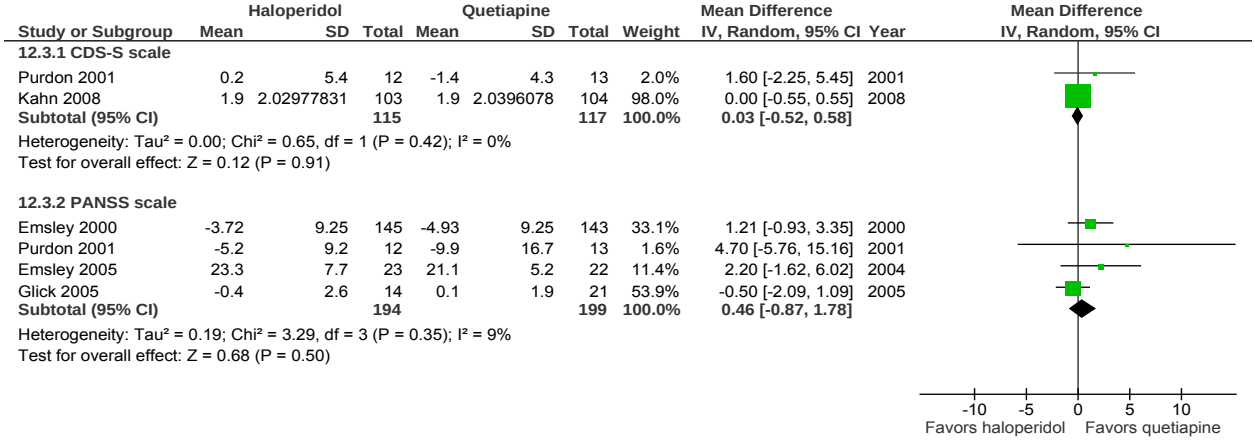
Two trials[91,123] (n = 232) reported no significant difference between groups using CDS–S (Table 40; Figure 19). There was no statistical heterogeneity across these two studies. Both studies included mixed populations with respect to disorder subtype and treatment resistance.

One trial[123] specifically excluded patients with comorbid drug or alcohol use. Doses of haloperidol varied from 1–4 mg/d[91] to 10–20 mg/d;[123] doses of quetiapine ranged from 200–750 mg/d[91] and 300–600 mg/d.[123] Duration of followup was ≥6 months in both studies. Risk of bias was high[91] and unclear;[123] both studies were industry-funded.

One of the trials described immediately above[123] (n = 25) reported results for the Beck Depression Inventory and found no significant difference between groups (Table 40).

The SoE for PANSS (general psychopathology) and CDS–S was graded as low, while the SoE for BDI was insufficient (Table 41).

Figure 19. Haloperidol versus quetiapine – General psychopathology



CDS–S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Scores

Nine studies[46,47,65,68,73,79,80,91,123] (n = 1,516) examined total scores using five scales (Table 40; Figure 20). Six trials[65,68,79,80,91,123] (n = 1,048) reported no significant difference using PANSS (total) (Table 40; Figure 20); there was minimal statistical heterogeneity. One study[80] specifically included patients with schizoaffective disorders. One study[79] included only patients with treatment resistance based on history. One study[123] specifically excluded patients with comorbid drug or alcohol use. Doses of haloperidol ranged from 1–4 mg/d[91] to 10–20 mg/d;[123] doses of quetiapine ranged from 50–800 mg/d across studies. Duration of followup was 6 weeks,[68] between 6 weeks and 6 months,[65,79] and >6 months.[80,91,123] Risk of bias was unclear for three studies[79,80,123] and high for three;[65,68,91] all were industry-funded.

Four trials[46,68,79,91] reported a significant difference favoring haloperidol using CGI–S; the results were statistically homogeneous. All studies included mixed populations in terms of disorder subtype and comorbid drug or alcohol use. One study[79] only included treatment-resistant patients. Dose of haloperidol ranged from 1–20 mg/d with varying ranges across studies. Likewise, quetiapine ranged from 75–800 mg/d. Duration of followup was 6 weeks,[46,68], 12 weeks,[79] and 1 year.[91] Risk of bias was unclear for two trials[46,79] and high for two trials;[68,91] all trials were industry-funded.

Four trials[46,47,73,79] reported no difference using BPRS (Table 40; Figure 20); the results were statistically homogeneous. All studies included mixed populations in terms of disorder subtypes. Two studies[47,73] excluded patients with comorbid drug or alcohol use. Two studies[73,79] included only patients with treatment resistance. One study[47] included only women. Doses of haloperidol and quetiapine were relatively consistent, although ranged from 4–30 mg/d and 50–1200 mg/d,

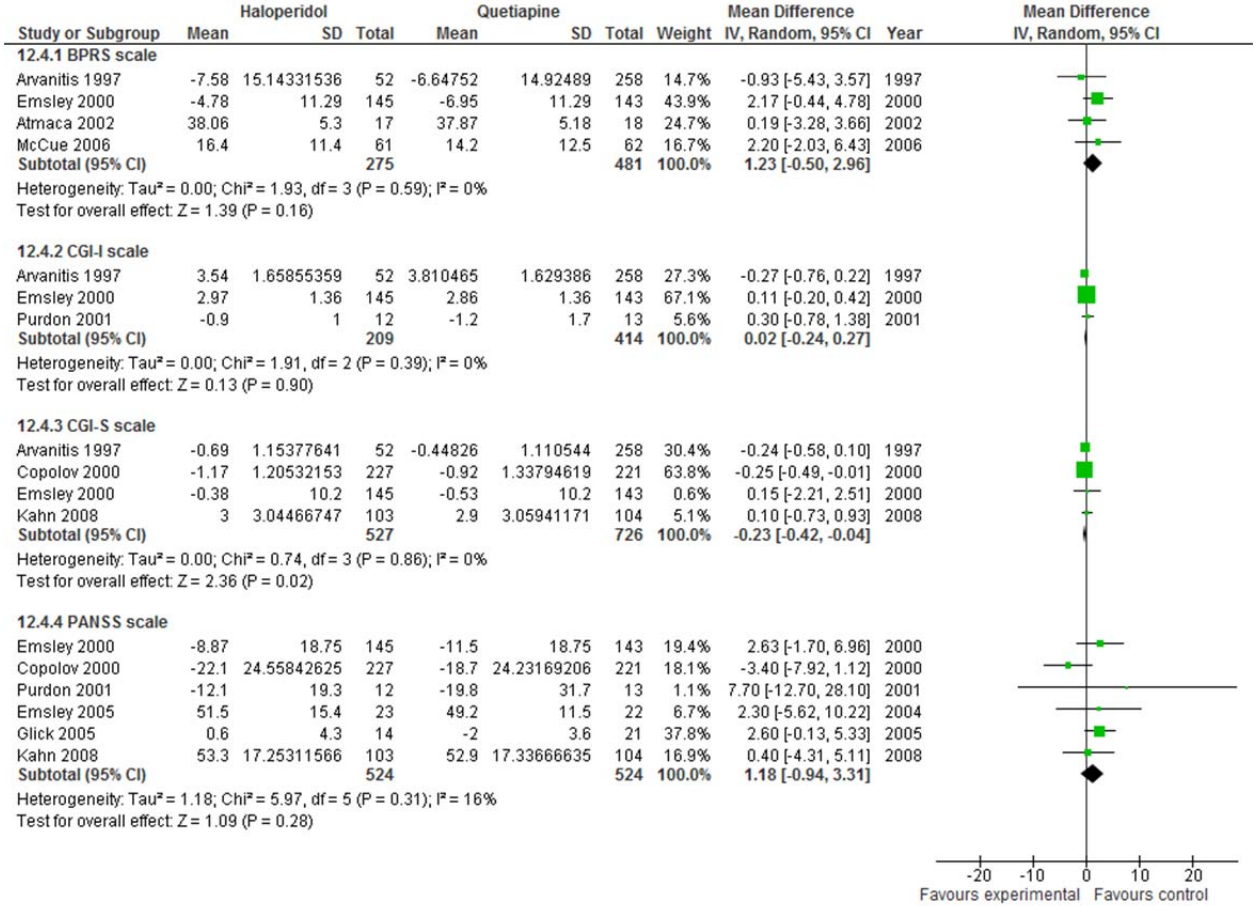
respectively, in one study.[73] Duration of followup was ≤6 weeks in three studies[46,47,73] and 12 weeks in one study.[79] Risk of bias was unclear for three trials and high for one.[73] Two trials[46,79] were industry-funded; two[47,73] did not report source of funding.

Three trials[46,79,123] (n = 623) showed no significant difference using CGI–I (Table 40; Figure 20); results were homogeneous across trials. All trials included mixed populations in terms of disorder subtypes. One study[123] excluded patients with comorbid drug or alcohol use. One study[79] included only patients with treatment resistance by history. Doses of haloperidol ranged from 5–20 mg/d; doses of quetiapine ranged from 75–750 mg/d. Risk of bias was unclear in all studies; all were industry-funded.

A single trial[91] (n = 207) compared 1–4 mg/d haloperidol with 200–750 mg/d quetiapine and found no significant difference between groups using GAF (Table 40; Figure 20). The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

The SoE for CGI–S was graded as moderate (favoring haloperidol), for BPRS, CGI–I, and PANSS was graded as low (no difference), and for GAF was graded as insufficient (Table 41).

Figure 20. Haloperidol versus quetiapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Sexual Dysfunction

One trial[91] (n = 207) comparing 1–4 mg/d haloperidol with 200–750 mg/d quetiapine found no significant difference between groups with respect to sexual dysfunction (Table 40). The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

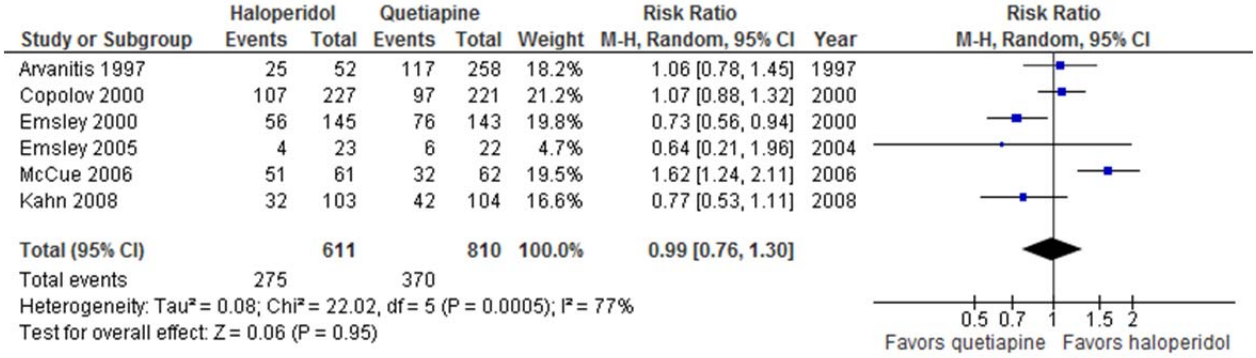
Health Care System Utilization

The same trial[91] described immediately above found no significant difference between groups for rates of hospitalization or rehospitalization (Table 40).

Other Outcomes

Pooled results for six trials[46,68,73,79,80,91] (n = 1,421) showed no significant difference in response rates (Table 40; Figure 21); however, the statistical heterogeneity was substantial (I^2 = 77 percent). We conducted predefined subgroup and sensitivity analyses to identify reasons for heterogeneous results across studies (Appendix M, Table 104). Heterogeneity was not explained by disorder subtypes or risk of bias. Three studies that followed patients for ≥6 months were homogeneous (I^2 = 0 percent), and pooled results favored quetiapine. Four studies that included both treatment-resistant and nonresistant patients showed reduced heterogeneity (I^2 = 6 percent), but no difference between groups. We examined one study[73] that was an outlier in that it showed a statistically significant benefit favoring haloperidol. This study was distinct from the others as it included doses of haloperidol ranging to 30 mg/d and it specifically excluded patients with comorbid drug or alcohol use. Further, the study did not report its source of funding, whereas the others declared industry support.

Figure 21. Haloperidol versus quetiapine – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

One trial[91] (n = 207) comparing 1–4 mg/d haloperidol with 200–750 mg/d quetiapine found no significant difference in remission rates (Table 40) or health-related quality of life. The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid

drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

Key Question 5. Subgroups

Sex

One trial[47] (n = 35) in female schizophrenic patients showed no significant difference for the global rating scale BPRS.

Treatment Resistance

One trial[79] (n = 288) in patients with treatment-resistant schizophrenia showed no significant difference on PANSS (positive), PANSS (negative), PANSS (general psychopathology), and general ratings and total scores (BPRS,[79] CGI–I,[79] CGI–S,[79] PANSS (total)).

Table 40. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[65,79,80,123]	4	393	0.68 (-0.14, 1.50)	0%	ND
Negative Symptoms					
PANSS[65,79,80,123]	4	393	1.36 (-0.41, 3.13)	76%	ND
SANS[46]	1	310	-0.94 (-2.04, 0.15)	NE	ND
General Psychopathology					
BDI[123]	1	25	5.30 (-2.79, 13.39)	NE	ND
CDS–S[91,123]	2	232	0.03 (-0.52, 0.58)	0%	ND
PANSS[65,79,80,123]	4	393	0.46 (-0.87, 1.78)	9%	ND
Global Ratings and Total Scores					
BPRS[46,47,73,79]	4	756	1.23 (-0.50, 2.96)	0%	ND
CGI–I[46,79,123]	3	623	0.02 (-0.24, 0.27)	0%	ND
CGI–S[46,68,79,91]	4	1253	-0.23 (-0.42, -0.04)	0%	haloperidol
GAF[91]	1	207	0.10 (-9.60, 9.80)	NE	ND
PANSS[65,68,79,80,91,123]	6	1048	1.18 (-0.94, 3.31)	16%	ND
Sexual Dysfunction					
Sexual dysfunction (UKU)[91]	1	207	1.01 (0.63, 1.62)	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[91]	1	207	1.01 (0.51, 2.01)*	NE	ND
Health-Related Quality of Life					
MANSA[91]	1	207	0.00 (-1.38, 1.38)	NE	ND
Other Outcomes					
Response rates[46,68,73,79,80,91]	6	1421	0.99 (0.76, 1.30)*	77%	ND
Remission rates[91]	1	207	0.72 (0.41, 1.25)*	NE	ND

Note: bolded results are statistically significant; * = binary outcome; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; I2 = I-squared; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 41. Strength of evidence (GRADE): haloperidol versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
BDI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CDS–S	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–I	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–S	4 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring haloperidol)
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	6 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence.

Haloperidol Versus Risperidone

Key Points:

- Thirty-three studies compared haloperidol with risperidone in patients with a range of illness severity.
- Twenty-two studies reported positive symptoms using two different scales: PANSS (20 studies) and SAPS (2 studies). Pooled results showed no differences between groups, and the SoE was considered low.
- Twenty-three studies assessed negative symptoms using two different scales: PANSS (20 studies) and SANS (4 studies). Pooled results of findings from each scale showed significant benefits for risperidone. The SoE was moderate for both scales.
- Sixteen studies reported general psychopathology using PANSS (general psychopathology; 16 studies), CDS–S (3 studies), HAM–D (2 studies), YMRS (2 studies), HAM–A (1 study), and MADRS (1 study). For PANSS, pooled results for all 16 studies are not presented due to substantial heterogeneity. Three studies were outliers in that they favored haloperidol; pooling the remaining 13 trials showed no difference between groups. Results for HAM–D and CDS–S showed no significant differences; however, heterogeneity was substantial. No differences were found for YMRS, MADRS, and HAM–A. The SoE was low for PANSS, CDS–S, HAM–D, and YMRS; insufficient for MADRS and HAM–A.
- Twenty-seven studies assessed global ratings and total scores using eight scales: PANSS (total; 20 studies), BPRS (13 studies), CGI–S (8 studies), CGI–I (3 studies), Nurses Observation Scale for Inpatient Evaluation (NOISIE) (1 study), Schedule for Affective Disorders and Schizophrenia–Change (SADS–C) (1 study), SCL–90–R (1 study), and Subjective Well–being Under Neuroleptic Scale (1 study). In all cases where there were multiple studies, pooled results showed no significant differences between groups. The

SoE was low for all scales except those with only one trial, which were considered insufficient.

- Response rates were assessed in 16 studies and showed no difference between groups.
- Relapse rates were assessed in six studies and showed a significant benefit for risperidone.
- Remission rates were assessed in two studies and showed no difference between groups.
- Two studies assessed health-related quality of life (HRQoL) and showed no significant differences between groups.
- Other outcomes were assessed in few trials and showed no differences between groups.

Thirty-three RCTs,[45,52,53,59-61,64,71-73,77,81,82,85,99,101,102,107,111,113,114,117,118,120,124,125,132,135,139,145,146,149,150] (n = 4,789) compared haloperidol with risperidone. Key characteristics of the included trials and summary findings are presented in Table 42 and Table 43. All studies included populations with mixed disorder subtypes. Five studies[72,73,81,132,145] specifically included patients with schizoaffective disorder, whereas two studies[52,114] excluded patients with schizoaffective disorder. One study[81] included only patients with first episodes, 13 studies[59,64,85,99,102,113,117,118,120,135,145,146,150] included only patients with multiple episodes, and the remaining studies included all patients. Five studies[73,99,145,146,150] included only patients with treatment resistance, which was ascertained by history in all but one study,[146] which conducted a run-in period to the trial. Four studies[72,81,118,124] included only patients with no treatment resistance. The remaining studies included all patients regardless of treatment resistance. Twenty studies[45,52,53,59,61,71,72,77,81,82,107,111,117,118,120,124,125,132,149,150] specifically excluded patients with comorbid drug or alcohol use; the remaining studies included patients both with and without comorbid drug or alcohol use. Six studies[102,107,111,117,149,150] included only patients of Asian descent. Doses of haloperidol ranged from 1 to 40 mg/d; doses ranged greater than 20 mg/d in two studies.[73,145] Doses of risperidone ranged from 1 to 16 mg/d.

Duration of followup was ≤6 weeks in 8 studies,[45,52,53,59,71,73,81,139] between 6 weeks and 6 months in 13 studies,[60,61,64,102,107,111,114,117,120,145,146,149,150] and >6 months in 10 studies;[72,77,82,101,113,118,124,125,132,135] 2 studies[85,99] did not report length of followup. Risk of bias was high in 10 studies[45,71,73,77,82,111,114,135,139,149] and unclear in the others. Eighteen studies[53,59,61,64,77,82,85,99,101,113,114,118,124,125,132,145,146] were industry-funded, two[107,149] were funded by government, one[102] received institutional funding, and the others did not report funding source.

Publication bias was assessed for outcomes with at least 10 studies, and results are reported in the sections that follow. The SoE for the evaluated outcomes varied from insufficient to moderate mainly depending on the number of included trials (Table 44).

For each outcome, we examined whether differences existed for clinical characteristics (disorder subtypes, inclusion or exclusion of patients with schizoaffective disorder, sex, age group, race, comorbidities, previous exposure to antipsychotics, and treatment resistance), study characteristics (drug dose, followup period, and study sponsorship), and analytic methods (risk of bias and imputed data). When pooled estimates showed evidence of statistical heterogeneity, we report on any subgroups that had an effect on heterogeneity. All other subgroups showed no effect. Appendix M Tables 105 to 111 provides detailed tables on all subgroup analyses.

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Apiquian et al. 2008[45] RCT (4 wks)	G1: HAL (2mg/d); (10) G2: RIS (1mg/d); (10)	Sz with psychosis	High, NR
Blin et al. 1996[52] RCT (4 wks)	G1: HAL (4–12mg/d); (20) G2: RIS (4–12mg/d); (21)	Sz with acute exacerbation and anxiety symptoms; no depot AP <1 mo or short–acting AP <2 d	Unclear, NR
Borison et al. 1992[53] RCT (6 wks)	G1: HAL (4–20mg/d); (12) G2: RIS (2–10mg/d); (12) Run-in phase: 1 wk	Sz with acute exacerbation defined by DSM–III–R	Unclear, Industry
Cavallaro et al. 2001[59] RCT (6 wks)	G1: HAL (2.5–10mg/d); (16) G2: RIS (2.5–10mg/d); (17) Run-in phase: <=1 wk	Subchronic Sz; no AP <1 wk or depot APs in <1 mo	Unclear, Industry
Ceskova et al. 1993[60] RCT (8 wks)	G1: HAL (2–20mg/d); (31) G2: RIS (2–20mg/d); (31)	Acute Sz pts defined by ICD–9	Unclear, NR
Chouinard et al. 1993[61] RCT (8 wks)	G1: HAL (20mg/d); (21) G2: RIS (2mg/d); (24) G3: RIS (6mg/d); (22) G4: RIS (10mg/d); (22) G5: RIS (16mg/d); (24) Washout period: 2 d – 2 wks	Sz; no depot AP for one tx cycle	Unclear, Industry
Claus et al. 1992[64] RCT (12 wks)	G1: HAL (1–10mg/d); (21) G2: RIS (1–10mg/d); (21) Washout period: 1 wk Run-in phase: 2 wks	Chronic Sz	Unclear, Industry
Crespo-Facorro et al. 2006[71] RCT (6 wks)	G1: HAL (3–9mg/d); (56) G3: RIS (3–6mg/d); (61) Washout period: 3–5 d	Sz with no AP <6 wks	High, Multiple sources
Csernansky et al. 2002 [72] RCT (12 mo)	G1: HAL (5–20mg/d); (188) G2: RIS (2–8mg/d); (177) Washout period: <1 wks	Sz or schizoaffective disorder; no hx of AP refractoriness or depot AP for one tx cycle; clinically stable >30 d	Unclear, Industry
de Sena et al. 2003[77] RCT (12 mo)	G1: HAL (5–17mg/d); (13) G2: RIS (1–6mg/d); (20) Washout period: 3–7d	Sz pts defined by DSM–III–R	High, Industry
Emsley et al. 1999[81] RCT (6 wks)	G1: HAL (2–10mg/d); (84) G2: RIS (2–10mg/d); (99)	Sz/ schizophreniform disorder without prior tx; psychotic symptoms requiring tx	Unclear, NR
Fakra et al. 2008[82] RCT (50 wks)	G1: HAL (NR); (15) G2: RIS (NR); (15) Washout period: 1 wk	Sz defined by DSM–IV	High, Multiple sources including industry
Heck et al. 2000[85] RCT (NR)	G1: HAL (3–24mg/d); (37) G2: RIS (2–16mg/d); (40)	Clinically stable Sz on AP; >5 on ESRS or antiparkinson drug use	Unclear, Industry
Kee et al. 1998[99] RCT (NR)	G1: HAL (15mg/d); (9) G2: RIS (6mg/d); (9) Washout period: <1 wks Run-in phase: 3 wks	Sz; tx resistant defined by DSM–III–R	Unclear, Multiple sources
Keefe et al. 2006[101] RCT (52 wks)	G1: HAL (2–19mg/d); (97) G2: RIS (2–10mg/d); (158)	Sz/ schizoaffective disorder; no previous AP <1 mo	Unclear, Industry
Kim et al. 2010[102] RCT (8 wks)	G1: HAL (15.9±7.1mg/d); (35) G2: RIS (4.8±2.9mg/d); (41) Washout period: >4wks	Sz not further defined	Unclear, Foundation
Lee et al. 2007[107] RCT (8 wks)	G1: HAL (7.6±2.6mg/d); (10) G2: RIS (4.1±0.8mg/d); (10)	Sz defined by DSM–IV	High, Government

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Liu 2000[111]	G1: HAL (7.6±2.6mg/d); (28) G2: RIS (4.1±0.8mg/d); (28)	PANSS (total) >65; no pts with hx of physical illness or substance abuse	High, NR
Marder et al. 1994[114] RCT (8 wks)	G1: HAL (20mg/d); (66) G2: RIS (2mg/d); (63) G3: RIS (6mg/d); (64) G4: RIS (10mg/d); (65) G5: RIS (16mg/d); (64) Washout period: 1 wk	Sz; no schizoaffective disorder	High, Industry
Marder et al. 2003[113] RCT (2 yrs)	G1: HAL (2 mg t.i.d. for 1 wk then 6 mg h.s.); (30) G2: RIS (2 mg t.i.d. for 1 wk then 6 mg h.s.); (33) Run-in phase: 2 wk	>2 Sz episodes <2 yrs w/ continuing psychotic symptoms; OP >1 mo	Unclear, Multiple sources
McCue et al. 2006[73] RCT (3 wks)	G1: HAL (4–30mg); (61) G2: RIS (2–9 mg); (65)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Min et al. 1993[117] RCT (8 wks)	G1: HAL (2.5–5mg/d); (19) G2: RIS (2.5–5mg); (16) Washout period:1 wk	Chronic Sz defined by DSM–III–R	Unclear, NR
Moller et al. 2008[118] RCT (2 yrs)	G1: HAL (2–8mg/d); (146) G2: RIS (2–8mg/d); (143) Washout period: 1 wk	Sz recovered from a 1st episode (1st inpatient tx of psychotic symptoms)	Unclear, Multiple sources
Peuskens et al. 1995[120] RCT (8 wks)	G1: HAL (10mg/d); (226) G2: RIS (1mg/d); (229) G3: RIS (4mg/d); (227) G4: RIS (8mg/d); (230) G5: RIS (12mg/d); (226) G6: RIS (16mg/d); (224) Washout period: 3–7 d	Chronic Sz defined by DSM–III–R	Unclear, NR
Purdon et al. 2000[124] RCT (54 wks)	G1: HAL (5–20mg/d); (23) G2: RIS (2–6mg/d); (21) Washout period: 2–9 d Run-in phase: 1 mo	Sz <5 yrs of 1st exposure to AP; mild symptom severity	Unclear, Industry
Remillard et al. 2008[125] RCT (12 mo)	G1: HAL (2–40mg/d); (14) G2: RIS (2–6mg/d); (14)	Sz defined DSM–III–R	Unclear, Industry
Schooler et al. 2005[132] RCT (2 yrs)	G1: HAL (1–8mg/d); (277) G2: RIS (1–8mg/d); (278) Washout period: 3–7 d	Sz, schizophreniform, or schizoaffective disorder <1 yr; <2 hospitalizations for psychosis; <12 wks of cumulative exposure to AP; required AP tx upon enrollment	Unclear, Industry
Shrivastava et al. 2000[135] RCT (12 mo)	G1: HAL (5–15mg/d); (50) G2: RIS (2mg/d); (50) Run-in phase: 2–4 wks	Hospitalized; acute Sz exacerbation	High, NR
Tamrakar et al. 2006[139] RCT (6 wks)	G1: HAL (10–20mg/d); (18) G2: RIS (4–6mg/d); (18) Washout period: 1 wk for oral; 4 wks for depot	Sz not further defined	High, NR
Volavka et al. 2002[145] RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: RIS (4–16mg/d); (41)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Wirshing et al. 1999[146] RCT (8 wks)	G1: HAL (15mg/d); (33) G2: RIS (6mg/d); (34) Washout period: 3–7 d Run-in phase: 3 wks	Tx resistant Sz; no functioning within last 5 yrs	Unclear, Multiple sources
Yen et al. 2004[149] RCT (12 wks)	G1: HAL (4–20mg/d); (20) G2: RIS (2–12mg/d); (21) Washout period: 7 d for oral AP; 4 wks for depot AP	Sz defined by DSM–III–R	High, Government
Zhang et al. 2001[150] RCT (12 wks)	G1: HAL (6mg/d); (37) G2: RIS (20mg/d); (41) Run-in phase: 2 wks	Sz; full dose conventional AP >3 mo; duration of illness >5 yrs	Unclear, NR

AP(s) = antipsychotic(s); BP = bipolar; D = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; ESRS = Extrapyramidal Syndrome Rating Scale; G = group; HAL = haloperidol; Hx = history; ICD–9 = International Classification of Diseases, 9th edition; Mg = milligrams; Mo = month; NR = not reported; OP = outpatient; Pts = patients; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; T.i.d. = twice daily; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = years(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Twenty-two trials[52,61,64,71,72,81,101,102,107,111,114,117,118,120,124,125,132,135,139,145,149,150] (n = 4,266) reported on positive symptoms using two scales (Table 43). Across 20 trials,[52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150] (n = 4,043) there was no significant difference between groups on the PANSS (positive) (Table 43; Figure 22); however, there was substantial statistical heterogeneity among the studies (I^2 = 53 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations with respect to comorbid drug use (6 studies): significantly favored risperidone (I^2 = 0 percent);
- Mixed populations with respect to first versus multiple episodes (11 studies): significantly favored risperidone (I^2 = 34 percent);
- Followed patients for >6 weeks and <6 months (10 studies); no difference between groups (I^2 = 0 percent);
- Asian patients only (5 studies): no difference between groups (I^2 = 0 percent);
- No industry funding or no funding source reported (12 studies): significantly favored risperidone (I^2 = 28 percent);
- High risk of bias (5 studies): significantly favored risperidone (I^2 = 0 percent).

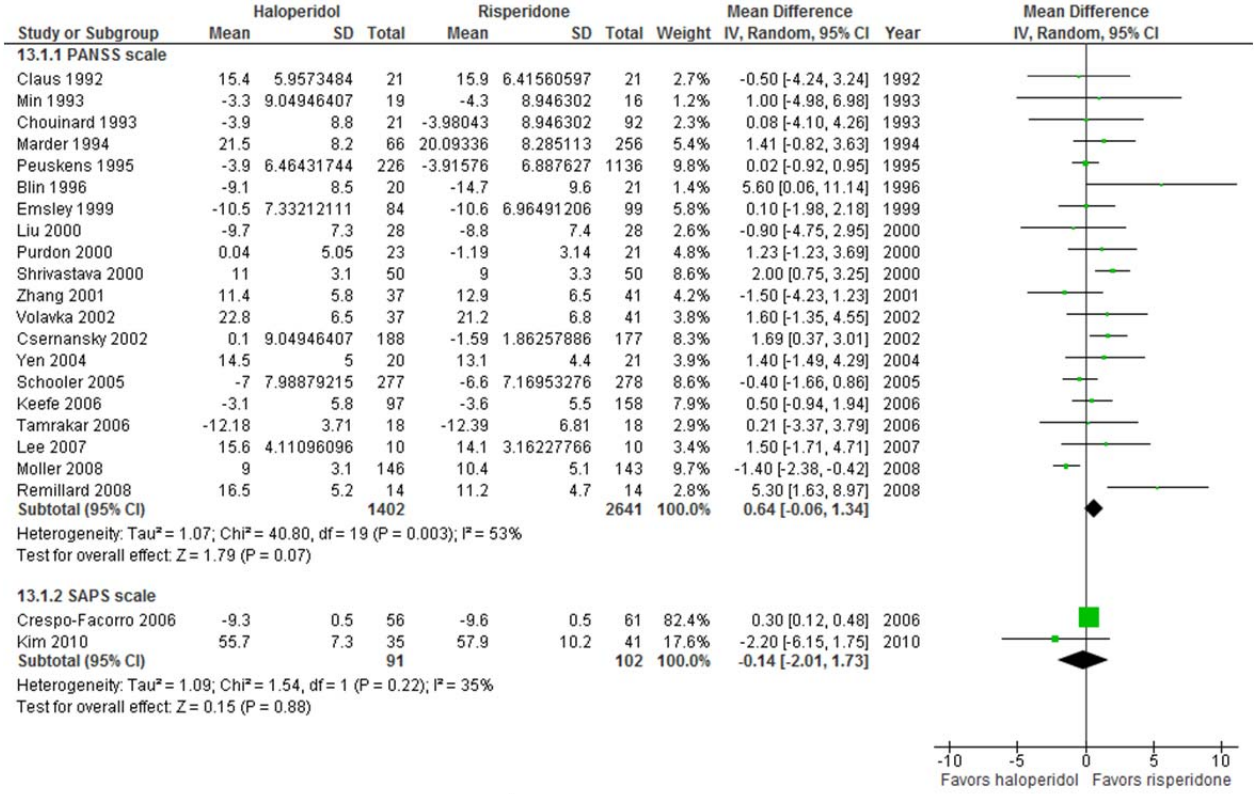
Tests for publication bias were not significant, although the funnel plot showed some asymmetry due to the two small studies that showed large effects for risperidone (Appendix K, Funnel plot 7).

Two trials[71,102] (n = 193) reported on the SAPS, (Table 43; Figure 22) and pooled results showed no significant difference between groups. Statistical heterogeneity was moderate (I^2 = 35 percent). Crespo-Facorro et al.[71] compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and showed a significant difference favoring risperidone. This study included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report on funding source. Kim et al.[102] compared 15.9±7.1

mg/d haloperidol with 4.8±2.9mg/d risperidone and found no significant difference between groups. This study included mixed populations in terms of disorder subtypes, comorbid drug or alcohol use, and treatment resistance. The study included only patients of Asian descent with multiple episodes. Duration of followup was 8 weeks; risk of bias was unclear, and the study received institutional support.

The SoE for PANSS (positive) and SAPS was graded as low (Table 44).

Figure 22. Haloperidol versus risperidone – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation

Negative Symptoms

Twenty-three trials[52,53,61,64,71,72,81,101,102,107,111,114,117,118,120,124,125,132,135,139,145,149,150] (n = 4,260) reported on negative symptoms using two scales (Table 43; Figure 23).

Twenty trials[52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150] (n = 4,043) reported PANSS (negative). Pooled results showed a significant difference favoring risperidone; statistical heterogeneity was moderate (I^2 = 30 percent). This was considered not to be clinically significant. Restricting the analyses to the following subgroups reduced the heterogeneity:

- Specifically included patients with schizoaffective disorder (4 studies): significantly favored risperidone (I^2 = 0 percent);
- Specifically excluded patients with schizoaffective disorder (2 studies): significantly favored risperidone (I^2 = 0 percent);
- Included patients with both first and multiple episodes (13 studies): significantly favored risperidone (I^2 = 0 percent);

- Mixed populations with respect to treatment resistance (14 studies): significantly favored risperidone (I^2 = 3 percent);
- Followed patients for <6 weeks (3 studies): no difference between groups (I^2 = 0 percent);
- Followed patients for >6 weeks and <6 months (10 studies); no difference between groups (I^2 = 0 percent);
- Received funding from sources other than industry or did not report source of funding (10 studies): significantly favored risperidone (I^2 = 0 percent).
- High risk of bias (5 studies): significantly favored risperidone (I^2 = 0 percent);
- Patient populations of Asian descent (5 studies): significantly favored risperidone (I^2 = 0 percent);

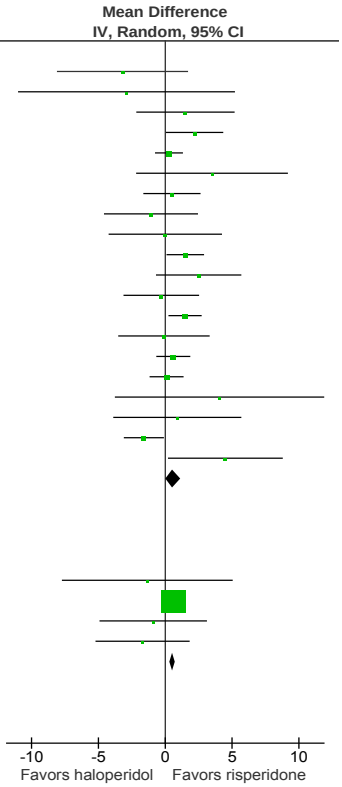
There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 8).

Pooled results from four trials[53,71,102,118] (n = 506) showed a significant difference on the SANS scale favoring risperidone. This was considered to be clinically significant. There was no evidence of heterogeneity (I^2 = 0 percent).

The SoE for PANSS (negative) and SANS was graded as moderate (Table 44).

Figure 23. Haloperidol versus risperidone – Negative symptoms

Study or Subgroup	Haloperidol Mean	SD	Total	Risperidone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
13.2.1 PANSS scale									
Claus 1992	22	7.79037868	21	25.2	8.24863625	21	1.4%	-3.20 [-8.05, 1.65]	1992
Min 1993	-7.4	9.11	19	-4.5	14.17	16	0.5%	-2.90 [-10.96, 5.16]	1993
Chouinard 1993	-2	7.7	21	-3.51087	7.462823	92	2.4%	1.51 [-2.12, 5.14]	1993
Marder 1994	24.3	7.7	66	22.10195	7.925187	256	5.8%	2.20 [0.10, 4.29]	1994
Peuskens 1995	-4.8	6.91531633	226	-5.07905	7.385917	1136	12.9%	0.28 [-0.72, 1.28]	1995
Blin 1996	-3.3	9.7	20	-6.8	8.6	21	1.1%	3.50 [-2.12, 9.12]	1996
Emsley 1999	-5.3	7.33212111	84	-5.8	6.96491206	99	5.8%	0.50 [-1.58, 2.58]	1999
Purdon 2000	-1.74	5.72	23	-0.67	5.99	21	2.6%	-1.07 [-4.54, 2.40]	2000
Liu 2000	-5.4	8	28	-5.4	8	28	1.8%	0.00 [-4.19, 4.19]	2000
Shrivastava 2000	14.3	3.3	50	12.8	3.6	50	9.9%	1.50 [0.15, 2.85]	2000
Zhang 2001	24.6	5.5	37	22.1	8.5	41	3.0%	2.50 [-0.65, 5.65]	2001
Volavka 2002	22.6	5.6	37	22.9	6.9	41	3.8%	-0.30 [-3.08, 2.48]	2002
Csernansky 2002	1.1	8.08967243	188	-0.38	1.86257886	177	11.2%	1.48 [0.29, 2.67]	2002
Yen 2004	17.2	5.5	20	17.3	5.5	21	2.7%	-0.10 [-3.47, 3.27]	2004
Schooler 2005	-4.2	7.32305947	277	-4.8	7.33626608	278	11.0%	0.60 [-0.62, 1.82]	2005
Keefe 2006	-1.5	4.8	97	-1.6	4.9	158	11.0%	0.10 [-1.12, 1.32]	2006
Tamrakar 2006	-13	9.11	18	-17.06	14.17	18	0.6%	4.06 [-3.72, 11.84]	2006
Lee 2007	16.4	6.00832755	10	15.5	4.74341649	10	1.5%	0.90 [-3.84, 5.64]	2007
Moller 2008	13.5	6.3	146	15.1	6.3	143	9.2%	-1.60 [-3.05, -0.15]	2008
Remillard 2008	25.6	6.6	14	21.1	4.7	14	1.8%	4.50 [0.26, 8.74]	2008
Subtotal (95% CI)			**1402**			**2641**	**100.0%**	**0.60 [0.01, 1.20]**	
Heterogeneity: Tau² = 0.45; Chi² = 27.17, df = 19 (P = 0.10); I² = 30%									
Test for overall effect: Z = 1.98 (P = 0.05)									
13.2.2 SANS scale									
Borison 1992	-1.83	4.4	12	-0.49	10.3	12	0.1%	-1.34 [-7.68, 5.00]	1992
Crespo-Facorro 2006	-1.4	0.6	56	-2	0.6	61	99.2%	0.60 [0.38, 0.82]	2006
Moller 2008	19.7	18	146	20.6	16.4	143	0.3%	-0.90 [-4.87, 3.07]	2008
Kim 2010	56.6	4.4	35	58.3	10.3	41	0.4%	-1.70 [-5.17, 1.77]	2010
Subtotal (95% CI)			**249**			**257**	**100.0%**	**0.58 [0.37, 0.80]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.57, df = 3 (P = 0.46); I² = 0%									
Test for overall effect: Z = 5.28 (P < 0.00001)									



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

General Psychopathology

Sixteen trials[52,61,64,81,107,111,117,118,120,124,132,135,139,145,149,150] (n = 3,073) reported PANSS (general psychopathology) (Table 43; Figure 24). Pooled results are not reported due to marked heterogeneity among the included trials (I^2 = 96 percent; 95% CI, 94 to 97). Thirteen of the trials

(n = 2,648) showed no difference between groups; pooled results also showed no difference and had no statistical heterogeneity (MD = 0.90; 95% CI, -0.10 to 1.90; $I^2 = 0$ percent). The three trials that were removed from the analysis all favored haloperidol. There was substantial statistical heterogeneity among these three trials. All three studies included mixed disorder subtypes. Two studies[118,135] only included patients with multiple episodes. One study[118] excluded patients with comorbid drug or alcohol use and treatment resistance; this study showed the most conservative estimate of the three favoring haloperidol. Doses of haloperidol were 2–8 mg/d,[118] 5–15 mg/d,[135] and 10–20[139] mg/d; doses of risperidone were 2–8 mg/d,[118] 2 mg/d,[135] and 4–6 mg/d.[139] Duration of followup was 6 weeks,[139] 1 year,[135]and 2 years.[118] Risk of bias was unclear for one study,[118] which was industry-funded; the other two studies had high risk of bias and did not report source of funding. There was no indication of publication bias based on statistical tests (Appendix K, Funnel plot 9). The SoE was graded as low (Table 44).

Three studies used CDS–S[71,85,118] (n = 483); pooled results showed no difference; however, there was substantial statistical heterogeneity. Crespo-Facorro[71] described immediately above showed a significant effect favoring risperidone. The other two studies showed no difference and were statistically homogeneous. Both studies included mixed disorder subtypes and only patients with multiple episodes. One study[118] excluded patients with treatment resistance, whereas the other included both treatment-resistant and nonresistant patients. One[118] excluded patients with comorbid drug or alcohol use, the other included a mixed population.[85] One study[118] used 2–8 mg/d of both drugs; the other compared 3–24 mg/d haloperidol with 2–16 mg/d risperidone. Duration of followup was 8 weeks in one study[118] and not reported in the other.[85] Both studies had unclear risk of bias and industry funding.

Two studies used HAM–D[71,118] (n = 468); pooled results showed no difference, although heterogeneity was substantial ($I^2 = 71$ percent). Crespo-Facorro et al.[71] compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and showed a significant difference favoring risperidone. This study included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report funding source. Moller et al.[118] compared 2–8 mg/d of both haloperidol and risperidone and found no difference between groups. The study included mixed populations in terms of disorder subtype. The study excluded patients with comorbid drug or alcohol use and treatment resistance; only patients with multiple episodes were included. Duration of followup was 2 years. Risk of bias was unclear, and the study was industry-funded.

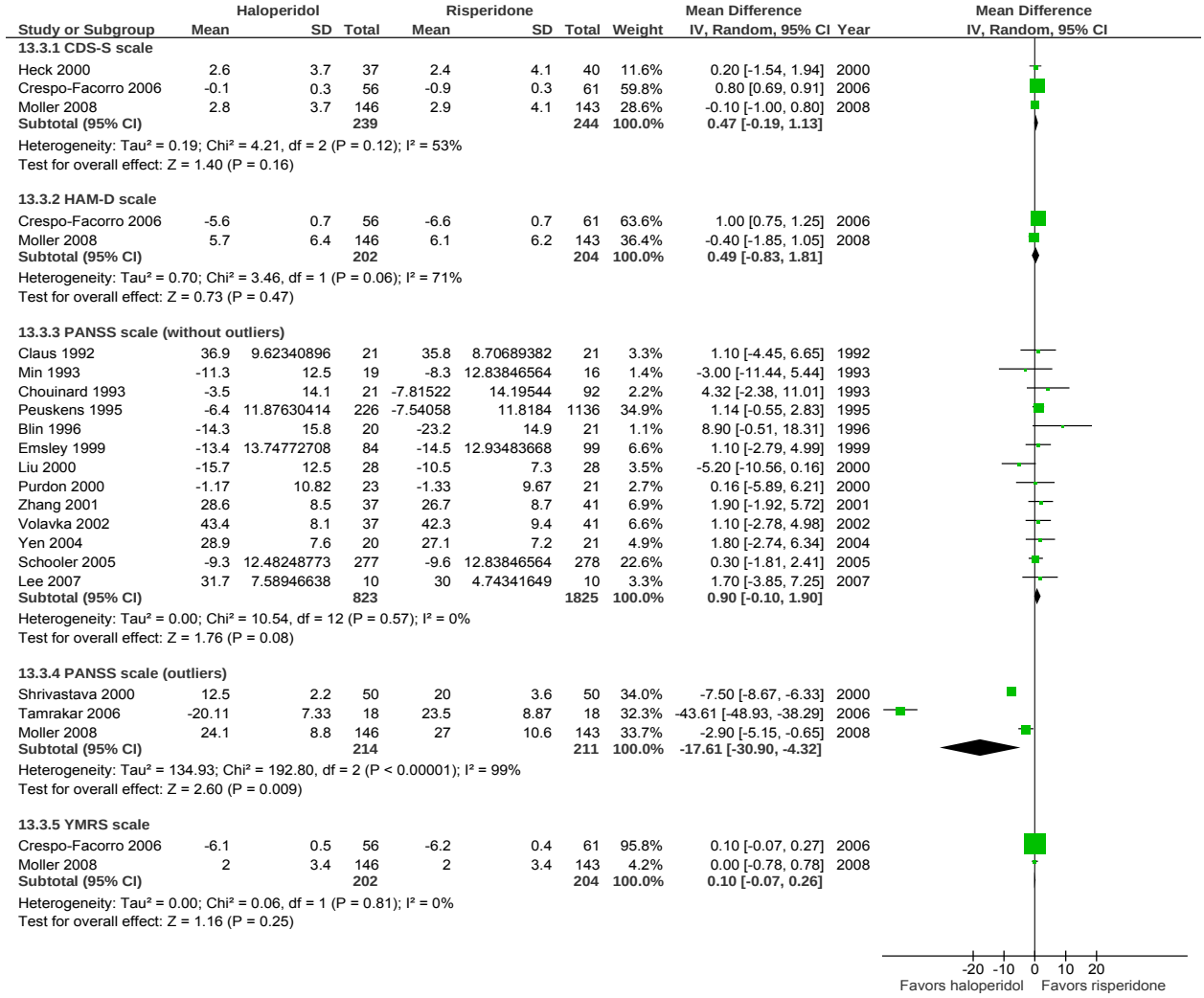
Two studies used the YMRS; results were consistent across studies and showed no difference between groups.[71,118] There was no evidence of heterogeneity between the studies ($I^2 = 0$ percent).

One trial used HAM–A[101] (n = 255) and found no difference between groups.

One study[101] (n = 256) compared 2–19 mg/d haloperidol with 2–10 mg/d risperidone and reported no difference between groups based on the MADRS.

The SoE for the CDS–S, HAM–D, PANSS, and YMRS were graded as low and for the HAM–A and MADRS were graded as insufficient (Table 44).

Figure 24. Haloperidol versus risperidone – General psychopathology



CDS–S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation; YMRS = Young Mania Rating Scale

Global Ratings and Total Scores

Global ratings and total scores were reported in 27 trials[45,52,53,60,61,64,71-73,81,82,85,101,107,111,113,114,117,118,120,132,135,139,145,146,149,150] (n = 4,557) using 8 different scales (Table 43; Figure 25).

Twenty studies (n = 4,021) used the PANSS (total).[45,52,61,64,72,81,82,101,107,111,114,117,118,120,132,135,139,145,149,150] There was no significant difference between groups; however, heterogeneity was substantial (I^2 = 75 percent). All studies individually showed no difference or favored risperidone except for one study[135] favoring haloperidol. When this study, was removed from the analysis, the heterogeneity was minimal (I^2 = 12 percent). This study compared 5–15 mg/d haloperidol with 2 mg/d risperidone and included mixed populations with respect to disorder subtype, treatment resistance, and comorbid drug or alcohol use. The study only included patients with multiple episodes. Duration of followup was 1 year. Risk of bias was high, and source of funding was not reported. There was some suggestion of publication bias based on Egger's test (p = 0.01) and visual inspection of the funnel plot, with one small study showing a large effect for risperidone (Appendix K, Funnel plot 10).

Thirteen studies (n = 2592) used the BPRS.[52,53,60,61,71,73,81,85,113,114,117,120,146] There was no significant difference between groups; statistical heterogeneity was moderate (I^2 = 44 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Excluded patients with comorbid drug or alcohol use (7 studies): significantly favored risperidone (I^2 = 0 percent);
- Included patients with multiple episodes only (5 studies): no difference between groups (I^2 = 0 percent);
- Duration of followup was ≤6 weeks (5 studies): significantly favored risperidone (I^2 = 0 percent);
- Industry funding (6 studies): no difference between groups (I^2 = 0 percent); Other sources of funding or source of funding not reported (7 studies): no difference between groups (I^2 = 18 percent);
- Unclear risk of bias (10 studies): no difference between groups (I^2 = 0 percent); High risk of bias (3 studies): significantly favored risperidone (I^2 = 7% percent);
- Some subgroups showed negligible heterogeneity, but the subgroups included very few studies (e.g., schizoaffective disorder, treatment resistance, and haloperidol >20 mg/d).

There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 11).

Eight studies reported scores based on CGI–S;[52,61,71,114,117,118,120,146] there were no differences between groups, but the results were statistically heterogeneous (I^2 = 63 percent). Most studies showed no difference between groups except for Crespo-Facorro et al.,[71] which favored haloperidol and Blin et al.,[52] which favored risperidone. Removing these two trials reduced the heterogeneity to 0 percent. Crespo-Facorro et al.[71] compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report funding source. Blin et al.[52] compared similar doses of haloperidol and risperidone (4–12 mg/d). The study excluded patients with schizoaffective disorder and comorbid drug or alcohol use, and included mixed populations with respect to treatment resistance and first or multiple episodes. Duration of followup was 4 weeks. Risk of bias was unclear; funding source was not reported.

Three studies used the CGI–I;[117,132,146] no difference between groups was found, but the studies were statistically heterogeneous (I^2 = 48 percent). One study[132] specifically included patients with schizoaffective disorder. Two studies[117,146] only included patients with multiple episodes. One study[146] only included patients with treatment resistance, ascertained by history and run-in to the trial. One study involved only Asian patients[117] and excluded patients with comorbid drug or alcohol use. Doses of haloperidol were 2.5–5 mg/d,[117] 1–8 mg/d[132] and 15 mg/d;[146] doses of risperidone were 2.5–5 mg/d,[117] 1–8 mg/d, [132] and 6 mg/d.[146] Duration of followup was 8 weeks[117,146] and 2 years.[132] All studies had unclear risk of bias, and two declared industry funding.[132,146]

Single studies[64] (n = 42) compared 1–10 mg/d of haloperidol with 1–10 mg/d of risperidone and found no differences between groups on the NOISIE or SADS–C.

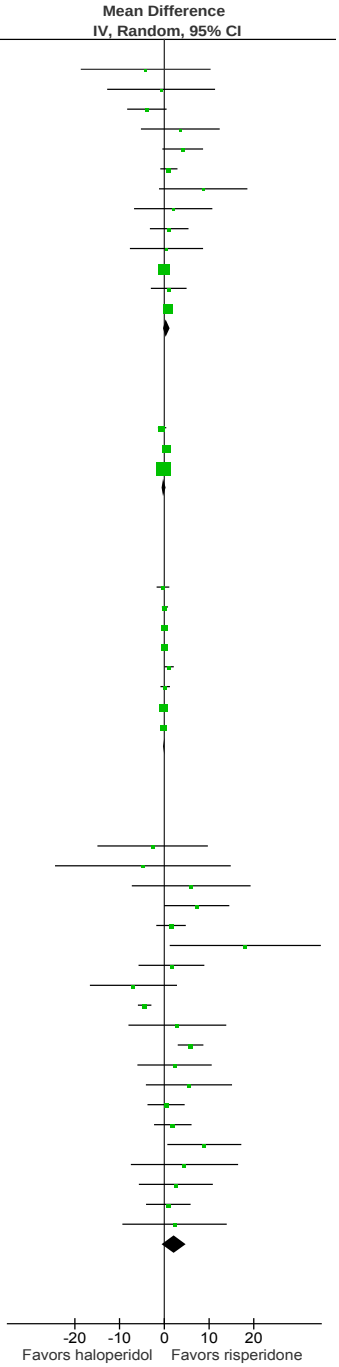
One study[114] (n = 322) compared 20 mg/d haloperidol with 2–16 mg/d risperidone and found a significant difference in favor of risperidone for the Symptom Checklist (SCL–90–R). The difference was considered not to be clinically important.

One study[118] (n = 289) compared 2–8 mg/d of haloperidol with 2–8 mg/d of risperidone and found no differences between groups on the Subjective Well–being Under Neuroleptic Scale.

The SoE was graded low for BPRS, CGI–I, CGI–S, and PANSS (total) and insufficient for NOISIE, SADS–C, SCL–90–R, and Subjective Well-being Under Neuroleptics Scale (Table 44).

Figure 25. Haloperidol versus risperidone – Global ratings and total scores

Study or Subgroup	Haloperidol Mean	SD	Total	Risperidone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
13.4.1 BPRS scale									
Borison 1992	40.18	18.4	12	44.35	17.49182	12	0.2%	-4.17 [-18.53, 10.19]	1992
Min 1993	-11.9	18.4	19	-11.2	17.49182	16	0.3%	-0.70 [-12.61, 11.21]	1993
Ceskova 1993	28.58	6.45860666	31	32.48	10.24468643	31	2.4%	-3.90 [-8.16, 0.36]	1993
Chouinard 1993	-5.4	18.4	21	-8.9913	17.49182	92	0.6%	3.59 [-5.05, 12.23]	1993
Marder 1994	51.2	16.4	66	47.09414	15.62803	256	2.3%	4.11 [-0.29, 8.50]	1994
Peuskens 1995	-8.1	12.32730303	226	-9.11664	12.99457	1136	11.0%	1.02 [-0.76, 2.79]	1995
Blin 1996	-17.1	15.6	20	-25.8	16.2	21	0.5%	8.70 [-1.03, 18.43]	1996
Wirshing 1999	59.3	18.4	33	57.3	17.49182	34	0.6%	2.00 [-6.60, 10.60]	1999
Emsley 1999	-16.8	14.66424222	84	-17.9	13.92982412	99	2.5%	1.10 [-3.07, 5.27]	1999
Heck 2000	39.1	18.4	37	38.6	17.49182	40	0.7%	0.50 [-7.53, 8.53]	2000
Marder 2003	-0.14	0.21908902	30	-0.14	0.22978251	33	41.6%	0.00 [-0.11, 0.11]	2003
McCue 2006	16.4	11.4	61	15.4	10.6	65	2.9%	1.00 [-2.85, 4.85]	2006
Crespo-Facorro 2006	-23.1	1.4	56	-23.9	1.4	61	34.2%	0.80 [0.29, 1.31]	2006
Subtotal (95% CI)			**696**			**1896**	**100.0%**	**0.51 [-0.17, 1.20]**	
Heterogeneity: Tau² = 0.29; Chi² = 21.56, df = 12 (P = 0.04); I² = 44%									
Test for overall effect: Z = 1.46 (P = 0.14)									
13.4.2 CGI-I scale									
Min 1993	2.8	1.16503219	19	3.3	1.16713324	16	17.2%	-0.50 [-1.28, 0.28]	1993
Wirshing 1999	3.5	1.16503219	33	3.1	1.16713324	34	26.7%	0.40 [-0.16, 0.96]	1999
Schooler 2005	2.62	1.16503219	277	2.69	1.16713324	278	56.0%	-0.07 [-0.26, 0.12]	2005
Subtotal (95% CI)			**329**			**328**	**100.0%**	**-0.02 [-0.39, 0.36]**	
Heterogeneity: Tau² = 0.06; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%									
Test for overall effect: Z = 0.10 (P = 0.92)									
13.4.3 CGI-S scale									
Min 1993	2.5	1.92	19	2.8	1.92601522	16	2.3%	-0.30 [-1.58, 0.98]	1993
Chouinard 1993	-0.5	1.1	21	-0.6413	1.291617	92	9.5%	0.14 [-0.40, 0.68]	1993
Marder 1994	3.4	1.2	66	3.273438	1.289899	256	16.1%	0.13 [-0.20, 0.46]	1994
Peuskens 1995	3.1	1.92	226	3	1.92601522	1136	18.5%	0.10 [-0.17, 0.37]	1995
Blin 1996	-1.2	1.4	20	-2.3	1.5	21	4.5%	1.10 [0.21, 1.99]	1996
Wirshing 1999	4.8	1.92	33	4.6	1.92601522	34	4.2%	0.20 [-0.72, 1.12]	1999
Crespo-Facorro 2006	-2.4	0.1	56	-2.2	0.1	61	27.5%	-0.20 [-0.24, -0.16]	2006
Moller 2008	3.3	1.3	146	3.4	1.3	143	17.4%	-0.10 [-0.40, 0.20]	2008
Subtotal (95% CI)			**587**			**1759**	**100.0%**	**0.03 [-0.17, 0.23]**	
Heterogeneity: Tau² = 0.04; Chi² = 18.70, df = 7 (P = 0.009); I² = 63%									
Test for overall effect: Z = 0.29 (P = 0.77)									
13.4.4 PANSS scale									
Claus 1992	74.3	20.16333306	21	76.9	20.16333306	21	3.0%	-2.60 [-14.80, 9.60]	1992
Min 1993	-21.9	27.7	19	-17.1	30.6	16	1.5%	-4.80 [-24.29, 14.69]	1993
Chouinard 1993	-9.3	27.7	21	-15.3065	27.55049	92	2.8%	6.01 [-7.11, 19.12]	1993
Marder 1994	88.8	26.4	66	81.54219	26.13288	256	5.4%	7.26 [0.13, 14.39]	1994
Peuskens 1995	-15	21.94861271	226	-16.5152	22.96741	1136	8.1%	1.52 [-1.64, 4.67]	1995
Blin 1996	-26.6	27.6	20	-44.7	27	21	1.9%	18.10 [1.38, 34.82]	1996
Emsley 1999	-29.3	24.74590875	84	-30.9	24.87468593	99	5.4%	1.60 [-5.61, 8.81]	1999
Liu 2000	-31.6	20.6	28	-24.7	15.7	28	4.1%	-6.90 [-16.49, 2.69]	2000
Shrivastava 2000	37.1	3.4	50	41.5	3.6	50	8.9%	-4.40 [-5.77, -3.03]	2000
Zhang 2001	64.7	16.6	37	61.8	30.6	41	3.6%	2.90 [-7.89, 13.69]	2001
Csernansky 2002	2.69	15.63089249	188	-3.17	10.51026641	177	8.3%	5.86 [3.14, 8.58]	2002
Volavka 2002	88.7	16.6	37	86.4	20.1	41	4.8%	2.30 [-5.85, 10.45]	2002
Yen 2004	66.2	16	20	60.7	14.9	21	4.1%	5.50 [-3.98, 14.98]	2004
Schooler 2005	-20.6	23.79994328	277	-21	24.34306472	278	7.5%	0.40 [-3.61, 4.41]	2005
Keefe 2006	-7.6	16.3	97	-9.5	15.5	158	7.5%	1.90 [-2.15, 5.95]	2006
Tamrakar 2006	-43.17	12.64	18	-52.11	12.2	18	4.8%	8.94 [0.82, 17.06]	2006
Lee 2007	68.1	15.8113883	10	63.6	10.75174404	10	3.2%	4.50 [-7.35, 16.35]	2007
Fakra 2008	57.27	12.92	15	54.7	9.5	15	4.8%	2.57 [-5.55, 10.69]	2008
Moller 2008	57.5	22.2	146	56.6	19.7	143	7.0%	0.90 [-3.94, 5.74]	2008
Apiquian 2008	-33.3	7.7	10	-35.6	16.9	10	3.3%	2.30 [-9.21, 13.81]	2008
Subtotal (95% CI)			**1390**			**2631**	**100.0%**	**2.23 [-0.37, 4.83]**	
Heterogeneity: Tau² = 19.27; Chi² = 77.00, df = 19 (P < 0.00001); I² = 75%									
Test for overall effect: Z = 1.68 (P = 0.09)									



BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Employment or Personal Earnings

One trial[135] (n = 100) comparing 5–15 mg/d haloperidol with 2 mg/d risperidone reported economic independence in patients and found no significant difference between groups (Table 43).

Encounters with Legal System

One trial[118] (n = 289) comparing 2-8 mg/d haloperidol with 2–8 mg/d risperidone reported attitudes regarding drugs and found no significant difference between groups (Table 43).

Health Care System Utilization

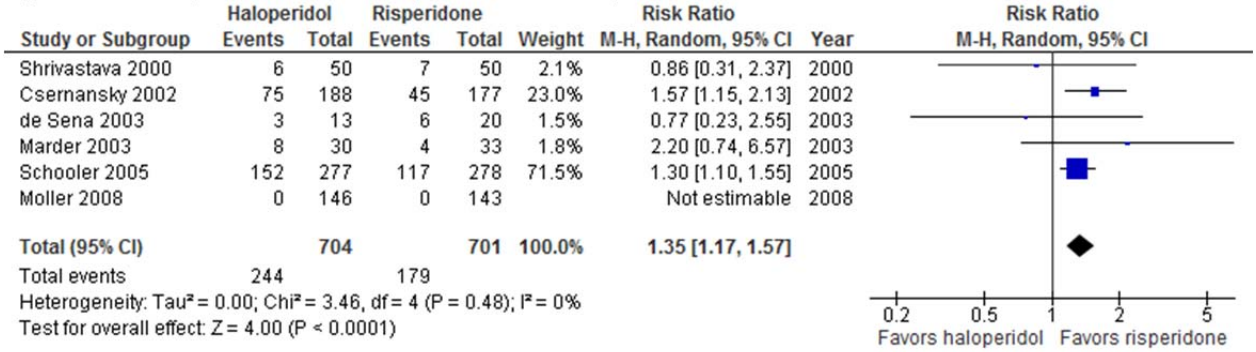
Pooled data from three trials[77,118,135] (n = 422) showed no significant differences between groups for rates of hospitalization or rehospitalization (I^2 = 24 percent) (Table 43). Two studies[77,118] excluded patients with comorbid drug or alcohol use. Two studies[118,135] only included patients with multiple episodes. One[118] study excluded patients with treatment resistance. Doses of haloperidol varied: 5–17 mg/d,[77] 2–8 mg/d,[118] and 5–15 mg/d;[135] doses of risperidone were 1–6 mg/d[77] 2–8 mg/d,[118] and 2 mg/d.[135] Duration of followup was 1 year[77,135] and 2 years.[118] Risk of bias was high for two trials[77,135] and unclear for one.[118] Two studies were industry-funded,[77,118] and one did not report funding source.

Other Outcomes

Relapse, Response, and Remission Rates

Pooled results from six trials[72,77,113,118,132,135] (n = 1,405) showed a significantly lower relapse rate favoring risperidone (Table 43; Figure 26); the studies were statistically homogeneous (I^2 = 0 percent).

Figure 26. Haloperidol versus risperidone – Relapse rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

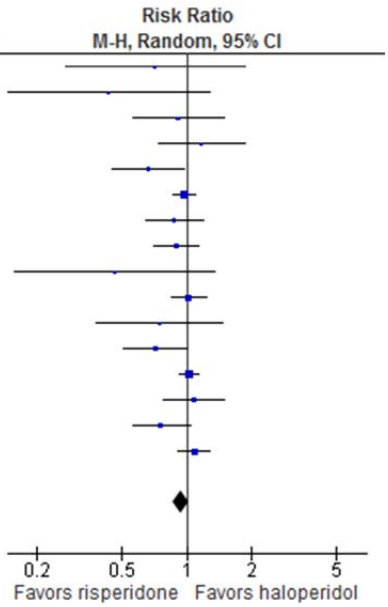
Two trials[60,71] (n = 179) showed no significant difference between groups on treatment remission rates (Table 43); results were statistically homogeneous (I^2 = 0 percent)

Pooled results from 16 trials[52,53,59,61,64,73,81,101,114,117,120,132,135,145,146,150] (n = 3,453) showed no significant difference between groups for treatment response rates (Table 43; Figure 27) there was no important statistical heterogeneity (I^2 = 29 percent). No important patterns were observed in the subgroup and sensitivity analyses; moreover, all subgroups showed no difference between groups (Appendix M, Table 111). All of the individual trials showed no differences except one study,[114] which showed a significant benefit favoring risperidone. This trial compared 20 mg/d haloperidol with 2–16 mg/d risperidone, excluded patients with schizoaffective disorder, and included mixed populations with respect to comorbid drug or alcohol use, first or multiple episodes, and treatment resistance. Length of followup was 8 weeks. Risk of bias was high, and the study was industry-funded. There was suggestion of publication bias with more small trials favoring risperidone, based on Begg's rank correlation (p = 0.03) and Egger's (p = 0.006) tests, as well as visual inspection of the funnel plot (Appendix K, Funnel plot 12).

Figure 27. Haloperidol versus risperidone – Response rates

Study or Subgroup	Haloperidol Events	Haloperidol Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Claus 1992	5	21	7	21	0.7%	0.71 [0.27, 1.89]	1992
Borison 1992	3	12	7	12	0.6%	0.43 [0.14, 1.28]	1992
Chouinard 1993	10	21	48	92	2.5%	0.91 [0.56, 1.49]	1993
Min 1993	14	19	10	16	2.8%	1.18 [0.74, 1.88]	1993
Marder 1994	20	66	117	256	3.8%	0.66 [0.45, 0.98]	1994
Peuskens 1995	133	226	687	1136	17.1%	0.97 [0.86, 1.10]	1995
Blin 1996	15	20	18	21	5.6%	0.88 [0.64, 1.19]	1996
Emsley 1999	47	84	62	99	8.0%	0.89 [0.70, 1.14]	1999
Wirshing 1999	4	33	9	34	0.6%	0.46 [0.16, 1.34]	1999
Shrivastava 2000	41	50	40	50	11.0%	1.02 [0.85, 1.24]	2000
Cavallaro 2001	7	16	10	17	1.4%	0.74 [0.38, 1.47]	2001
Zhang 2001	20	37	31	41	4.7%	0.71 [0.51, 1.01]	2001
Schooler 2005	203	277	197	278	18.8%	1.03 [0.93, 1.15]	2005
Crespo-Facorro 2006	32	56	32	61	5.0%	1.09 [0.78, 1.51]	2006
Keefe 2006	35	97	75	158	5.5%	0.76 [0.56, 1.04]	2006
McCue 2006	51	61	50	65	12.2%	1.09 [0.91, 1.29]	2006
Total (95% CI)		**1096**		**2357**	**100.0%**	**0.94 [0.87, 1.02]**	
Total events	640		1400				

Heterogeneity: Tau² = 0.01; Chi² = 21.13, df = 15 (P = 0.13); I² = 29%
Test for overall effect: Z = 1.37 (P = 0.17)



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Medication Adherence

Three trials[72,101,149] (n = 661) assessed medication adherence (Table 43); pooled results were homogeneous (I^2 = 0 percent) and showed no difference between groups.

Health-related Quality of Life

Two trials[113,118] (n = 674) assessed health-related quality of life using a variety of measures and found no differences (Table 43).

Patient Satisfaction

One trial[146] (n = 67) comparing 15 mg/d haloperidol with 6 mg/d risperidone found no significant differences between groups for patient satisfaction (Table 43).

Key Question 5. Subgroups

Race

Six trials[102,107,111,117,149,150] (n = 369) in Asian patients showed no significant difference on PANSS (positive), SAPS, PANSS (negative), or SANS.

First Episode

Pooled results from four trials[71,81,118,132] (n = 1,365) in patients undergoing treatment for their first psychotic episode showed a significant difference on the SAPS and SANS scales favoring risperidone ([MD = 0.30; 95% CI, 0.12 to 0.48] and [MD = 0.60; 95% CI, 0.38 to 0.62], respectively). No significant differences were found for the PANSS (positive), CDS–S, HAM–D, PANSS (negative), PANSS (general psychopathology), BPRS, CGI–I, CGI–S, PANSS (total), and YMRS.

Table 43. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150]	20	4043	0.64 (-0.06, 1.34)	53%	ND
SAPS[71,102]	2	193	-0.14 (-2.01, 1.73)	35%	ND
Negative Symptoms					
PANSS[52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150]	20	4043	0.60 (0.01,1.20)	30%	risperidone
SANS[53,71,102,118]	4	506	0.58 (0.37, 0.80)	0%	risperidone
General Psychopathology					
CDS–S[71,85,118]	3	483	0.47 (-0.19, 1.13)	53%	ND
HAM–A[101]	1	255	0.10 (-1.44, 1.64)	NE	ND
HAM–D[71,118]	2	406	0.49 (-0.83, 1.81)	71%	ND
MADRS[101]	1	255	0.50 (-1.58, 2.58)	NE	ND
PANSS (general psychopathology), omit outliers[52,61,64,81,107,111,117,120,124,132,145,149,150]	13	2648	0.90 (-0.10, 1.90)	0%	ND
YMRS[71,118]	2	406	0.10 (-0.07, 0.26)	0%	ND
Global Ratings and Total Scores					
BPRS[52,53,60,61,71,73,81,85,113,114,117,120,146]	13	2592	0.51 (-0.17, 1.20)	44%	ND
CGI–I[117,132,146]	3	657	-0.02 (-0.39, 0.36)	48%	ND
CGI–S[61,71,114,117,118,120,146]	8	1667	0.03 (-0.18, 0.23)	61%	ND
NOSIE–30[64]	1	42	-5.30 (-21.61, 11.01)	NE	ND
PANSS[45,52,61,64,72,81,82,101,107,111,114,117,118,120,132,135,139,145,149,150]	20	4021	2.23 (-0.37, 4.83)	75%	ND
SADS–C[64]	1	42	-0.40 (-10.12, 9.32)	NE	ND
SCL–90–R[114]	1	63	0.31 (0.12, 0.50)	NE	risperidone
Subjective Well–being Under Neuroleptic Scale[118]	1	289	1.80 (-2.39, 5.99)	NE	ND
Employment or Personal Earnings					
Economic independence[135]	1	100	0.94 (0.68, 1.29)*	NE	ND
Encounters with legal system					
Attitude regarding drugs[118]	1	289	-0.80 (-2.12, 0.52)	NE	ND
Health care system utilization					

Table 43. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Relapse rates[72,77,113,118,132,135]	6	1405	1.35 (1.17, 1.57)*	0%	risperidone
Remission rates[60,71]	2	179	0.84 (0.56, 1.24)	0%	ND
Response rates[52,53,59,61,64,73,81,101,114,117,120,132,135,145,146,150]	16	3453	0.94 (0.87, 1.02)	29%	ND
Medication adherence[72,101,149]	3	661	0.99 (0.95, 1.02)*	0%	ND
Patient satisfaction[146]	1	67	0.67 (0.37, 1.20)*	NE	ND
Health-Related Quality of Life					
QLS: Total[113]	1	63	0.10 (-0.17, 0.37)	NE	ND
LQLP: total score[118]	1	289	0.10 (-0.20, 0.40)	NE	ND
LQLP: general health[118]	1	289	-0.10 (-0.43, 0.23)	NE	ND
QoL: common objects[113]	1	63	0.04 (-0.25, 0.33)	NE	ND
QoL: Intrapsychic[113]	1	63	0.09 (-0.14, 0.32)	NE	ND
QoL: role functioning[113]	1	63	0.05 (-0.69, 0.79)	NE	ND

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; LQLP = Lancashire Quality of Life Profile; MADRS = Montgomery–Asberg Depression Rating Scale; ND = no difference; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale; QoL = quality of life; SADS–C = Schedule for Affective Disorders and Schizophrenia–Change; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL–90–R = Symptom Checklist–90–R; SWBUN = Subjective Well-Being Under Neuroleptics Scale; YMRS = Young Mania Rating Scale

Table 44. Strength of evidence (GRADE): haloperidol versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	20 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	20 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring risperidone)
SANS	4 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring risperidone)
General Psychopathology						
CDS–S	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM–A	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
HAM–D	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
MADRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–I	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–S	8 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
NOSIE–30	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

Table 44. Strength of evidence (GRADE): haloperidol versus risperidone (continued)

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings and Total Scores (continued)						
PANSS	20 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SADS–C	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
SCL–90–R	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
SWBUN	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Asberg Depression Rating Scale; ND = no difference; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; RoB = risk of bias; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; SADS–C = Schedule for Affective Disorders and Schizophrenia–Change; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL–90–R = Symptom Checklist–90–R; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Ziprasidone

Key Points:

- Eight RCTs compared haloperidol versus ziprasidone in patients with a range of disease severity.
- The most commonly reported outcome was global rating or total symptom scores using four different scales: BPRS (4 trials), CGI–S (4 trials), PANSS (4 trials), and GAF (3 trials). No differences were found between groups for any of the scales. The SoE was low for all scales.
- Six studies reported response rates and overall showed no difference; however, results showed substantial statistical heterogeneity, which was not fully explained through the predefined subgroup and sensitivity analyses. Moreover, some subgroups showed no differences (3 studies excluding patients with comorbid drug or alcohol use), one favored haloperidol (2 studies with duration of followup >6 months), and others favored ziprasidone (3 studies of patients with treatment resistance or mixed populations; 2 studies in which funding source was not reported).
- Three studies assessed remission rates and found no differences between groups.
- Other outcomes were assessed in only one to two studies, and in all but one case showed no differences between groups.

Eight RCTs[57,69,73,75,83,86,91,122] (n = 2,067) compared haloperidol with ziprasidone. Key characteristics of the included trials and summary findings are presented in Table 45 and Table 46. All trials included mixed populations in terms of disorder subtypes. Three studies[57,69,83] excluded patients with comorbid drug or alcohol use. One study included only patients with treatment resistance ascertained by history.[73] Three studies specifically excluded patients with treatment resistance.[57,86,91] Doses of haloperidol ranged across studies and varied from 1–4 mg/d[75,91] to 4–30 mg/day.[73] Doses of ziprasidone also varied across studies, ranging from 4–160 mg/d[83] to 40–240 mg/d.[73]

Duration of followup was ≤6 weeks in four studies[57,69,73,83] and ≥6 months in four studies;[75,86,91,122] one study[122] followed patients for 3.75 years. Risk of bias was unclear for two studies[73,122] and high for the others. Seven studies were industry-funded, whereas two studies[73,83] did not report their source of funding.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of trials (Table 47).

Table 45. Characteristics of RCTs comparing haloperidol versus ziprasidone in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Brook et al. 2005[57] RCT (6 wks)	G1: HAL IM (2.5–10mg/d; Oral: 5–20mg/d); (138) G2: ZIP IM (10–40mg/d; Oral: 40–80mg/d); (429)	Acute exacerbation of Sz or schizoaffective disorder	High, Industry
Corripio et al. 2005[69] RCT (2 wks)	G1: HAL (5–20mg/d); (10) G2: ZIP (10–40mg/d); (10) Washout period: 2 wks	Sz manifesting acute psychotic exacerbation	High, Multiple sources
Davidson et al. 2009[75] RCT (6 mo)	G1: HAL (1–4mg/d); (103) G2: ZIP (40–160mg/d); (82)	<2 yrs since onset of positive symptoms; <2 wks exposure to AP <1 yr; <6 wks lifetime exposure to AP	High, Industry
Goff et al. 1998[83] RCT (4 wks)	G1: HAL (15mg/d); (17) G2: ZIP (4mg/d); (19) G3: ZIP (10mg/d); (17) G4: ZIP (40mg/d); (17) G5: ZIP (160mg/d); (20) Washout period: ≥1 wks	Hospitalized ≤2 wks for acute exacerbation; hospitalized or resided in an intermediate tx center ≥3 mo; partially responded to AP tx; no depot AP ≤2 mo or recent illicit drug	High, NR
Hirsch et al. 2002[86] NRCT (28 wks)	G1: HAL (5–15mg/d); (153) G2: ZIP (80–160mg/d); (148) Washout period: 2 wks Run-in phase: ≤2 wks	Chronic/ subchronic Sz; required AP maintenance tx; ≤2 AP tx failures ≤2 yrs; received investigational AP ≤4 wks or FLU ≤5 wks	High, Industry
Kahn et al. 2008[91] RCT (12 mo)	G1: HAL (1–4mg/d); (103) G2: ZIP (40–160mg/d); (82)	Sz/ schizophreniform or schizoaffective disorder; ≤2 yrs since onset of positive symptoms; no AP ≥2 wks in last 1 yr, or ≥6 wks at any time	High, Industry
McCue et al. 2006[73] RCT (3 wks)	G1: HAL (4–30mg); (61) G2: ZIP (40–240 mg); (59)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Potkin et al. 2009[122] RCT (3.75 yrs)	G1: HAL (5–20mg/d); (151) G2: ZIP (80–120mg/d); (448) G3: ZIP (80–160mg/d) Washout period: 4 wks	Chronic/ subchronic Sz or schizoaffective disorder	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; D = day; FLU = fluphenazine; G = group; HAL = haloperidol; Hx = history; IM = intramuscular; Mg = milligrams; Mo = month; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wks = weeks; Yr(s) = year(s); ZIP = ziprasidone

Key Question 1. Improving Core Illness Symptoms

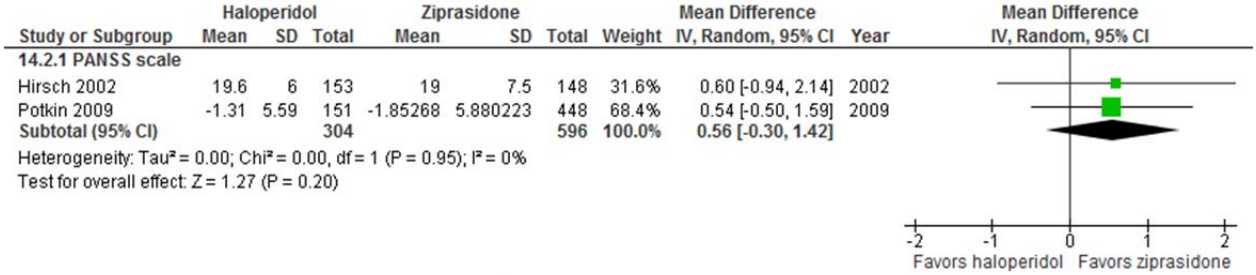
Positive Symptoms

None of the included trials reported positive symptoms.

Negative Symptoms

Two trials[86,122] (n = 900) assessed negative symptoms using the PANSS (negative) and reported no significant difference between groups (Table 46; Figure 28); results showed no evidence of heterogeneity (I^2 = 0 percent). Both studies included mixed populations with respect to disorder subtypes and comorbid drug or alcohol use. Both studies used consistent doses of haloperidol (5–15 mg/d and 5–20 mg/d) and ziprasidone (80–160 mg/d). One study[86] excluded patients with treatment resistance. Duration of followup was 28 weeks[86] and 3.75 years.[122] Risk of bias was high[86] and unclear;[122] both were funded by industry. The SoE was low (Table 47).

Figure 28. Haloperidol versus ziprasidone – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

One trial[57] (n = 567) compared 5–20 mg/d haloperidol with 10–40 mg/d ziprasidone and found no significant difference between groups using the Covi Anxiety Scale (Table 46). This trial included patients with mixed disorder subtypes. Patients with comorbid drug or alcohol use and those with treatment resistance were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

One trial[91] (n = 185) compared haloperidol (1–4 mg/d) with ziprasidone (40–60 mg/d) and found no significant difference between groups using the CDS–S (Table 46). The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded.

One trial[86] (n = 301) compared haloperidol (5–15 mg/d) with ziprasidone (80–160 mg/d) and found no significant difference between groups on MADRS (Table 46). The trial included a mix of disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 28 weeks. Risk of bias was high, and the trial was industry-funded.

The SoE was insufficient for three scales used to assess general psychopathology (Table 47).

Global Ratings and Total Scores

Seven trials assessed total scores using four different tools. Four trials[57,73,83,86] (n = 1,078) found no significant difference between groups on BPRS (Table 46; Figure 29); there was no statistical heterogeneity. All studies included a mix of disorder subtypes. Two studies[57,83] excluded patients with comorbid drug or alcohol use. One study[73] included only patients with treatment resistance; two studies[57,86] excluded patients with treatment resistance. Doses of haloperidol were relatively consistent, except for one study where the upper limit was 30 mg/d.[73] Upper limits for ziprasidone varied: 40 mg/d,[57] 160 mg/d,[83,86] and 240 mg/d.[73] Duration of

followup was ≤6 weeks in three studies and 28 weeks in the other.[86] Risk of bias was high in three studies and unclear in one.[73] Two studies[57,86] reported industry funding; two studies[73,83] did not report funding source.

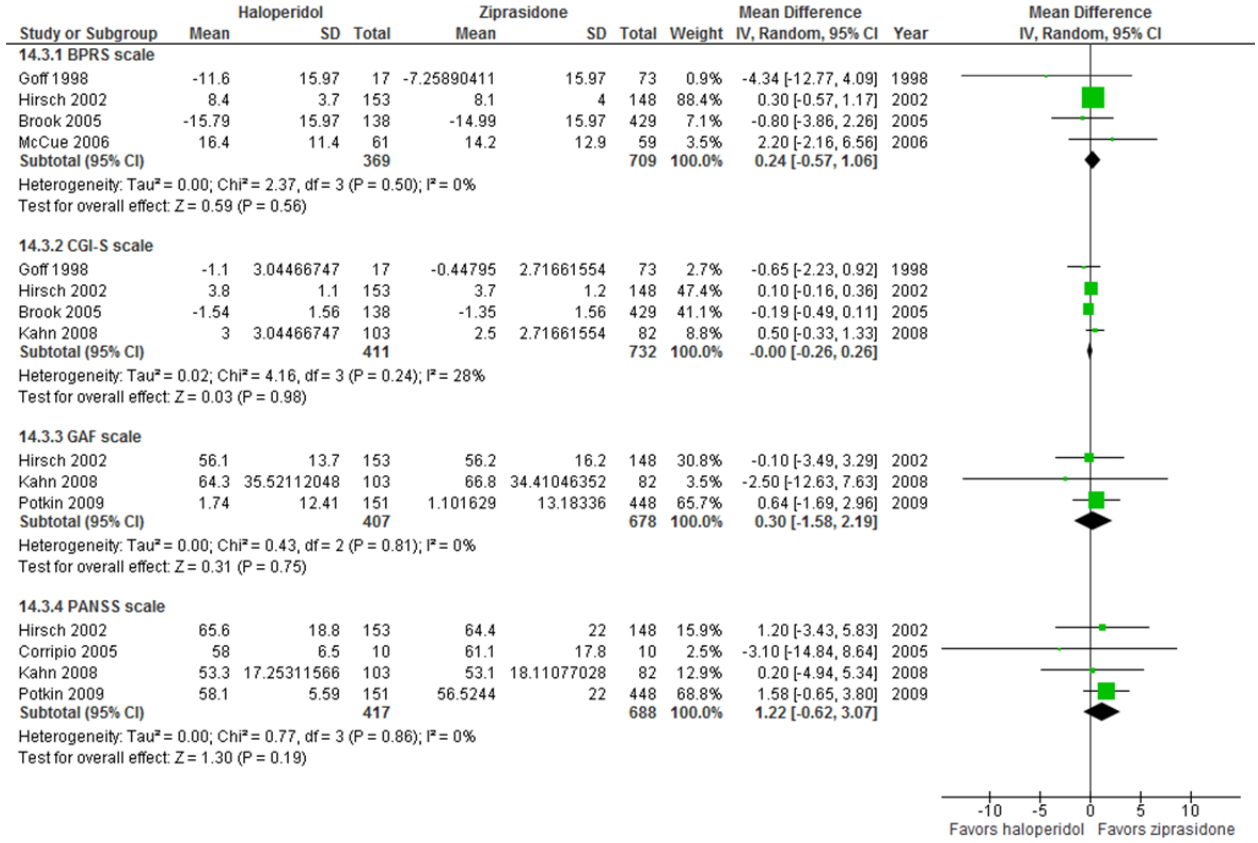
Four trials[57,83,86,91] (n = 1,275) showed no significant difference between groups on CGI–S (Table 46; Figure 29); there was some statistical heterogeneity between studies. All studies included a mix of disorder subtypes. Two studies[57,83] excluded patients with comorbid drug or alcohol use. Three studies[57,86,91] excluded patients with treatment resistance. One study[91] used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were relatively consistent; however, one study[57] had a lower maximum dose (40 vs. 160 mg/d). Duration of followup was ≤6 weeks in two studies,[57,83] 28 weeks in one study,[86] and 1 year in one study.[91] All studies were high risk of bias; three reported industry funding, and one did not report funding source.[83]

Four trials[69,86,91,122] (n = 1,105) showed no significant difference between groups on PANSS (total) (Table 46; Figure 29); there was no statistical heterogeneity among studies. All studies included a mix of disorder subtypes. One study[69] excluded patients with drug or alcohol use. Two studies[86,91] excluded patients with treatment resistance. One study[91] used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were relatively consistent; however, one study[69] had a lower maximum dose (40 vs. 160 mg/d). Duration of followup ranged from 2 weeks[69] to 3.75 years.[122] Risk of bias was high for three studies and unclear for one;[122] all studies were industry-funded.

Three trials[86,91,122] (n = 1,085) showed no significant difference between groups on the GAF scale (Table 46; Figure 29); there was no statistical heterogeneity. All studies included patients with a mix of disorder subtypes and comorbid drug or alcohol use. Two studies[86,91] excluded patients with treatment resistance. One study[91] used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were consistent across studies. Followup ranged from 28 weeks[86] to 3.75 years.[122] Risk of bias was high for two studies[86,91] and unclear for one;[122] all were industry-funded.

The SoE was graded as low for BPRS, CGI–S, PANSS (total), and GAF (Table 47).

Figure 29. Haloperidol versus ziprasidone – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; GAF = Global Assessment of Functioning; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Sexual Dysfunction

One trial[91] (n = 185) compared haloperidol (1–4 mg/d) and ziprasidone (40–160 mg/d) and found no differences between groups for incidence of sexual dysfunction (Table 46). The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded.

Health Care System Utilization

Pooled results for two trials[86,91] (n = 486) showed no significant difference between groups for rates of hospitalization or rehospitalization (Table 46). Both trials included patients with a mix of disorder subtypes and comorbid drug or alcohol use. Both excluded patients with treatment resistance. One trial[91] used a relatively lower dose of haloperidol (1–4 mg/d); ziprasidone doses were consistent. Duration of followup was 28 weeks[86] and 1 year.[91] Risk of bias was high in both trials, and both were industry-funded.

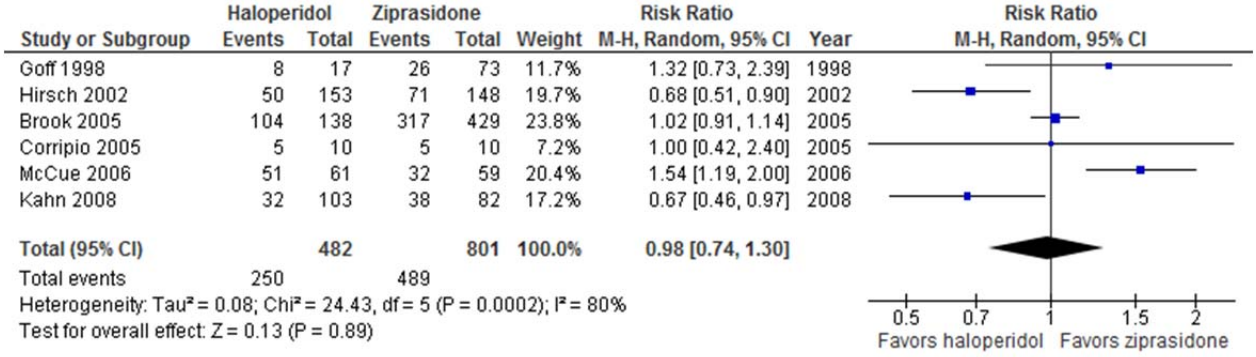
Other Outcomes

Response and Remission Rates

Six trials[57,69,73,83,86,91] (n = 1,283) showed no significant difference between groups for treatment response rates (Table 46; Figure 30). However, statistical heterogeneity was substantial; therefore, the overall estimate may not be meaningful. We conducted predefined subgroup and sensitivity analyses to explain heterogeneity (Appendix M, Table 112). Three studies that excluded patients with comorbid drug or alcohol use had no heterogeneity ($I^2 = 0$ percent) and showed no difference. Two studies that followed patients for ≥6 months had no heterogeneity ($I^2 = 0$ percent) and showed significant results favoring haloperidol. Three studies had mixed treatment-resistant and nonresistant patients (2 studies) or included only treatment-resistant patients (1 study); when combined, these studies had no heterogeneity ($I^2 = 0$ percent) and showed significant results favoring ziprasidone. Two studies did not report their source of funding; these studies had no heterogeneity, and their pooled results favored ziprasidone. One study[73] appeared as an outlier, as it showed a statistically significant benefit for ziprasidone. This study included relatively larger doses of haloperidol (up to 30 mg/d) and included only treatment-resistant patients; the study had unclear risk of bias.

Three trials[86,91,122] (n = 1,085) found no significant difference between groups for remission rates (Table 46); the statistical heterogeneity was minimal. These studies included a mix of populations with respect to disorder subtypes and cormorbid drug or alcohol use. Two studies[86,91] excluded patients with treatment resistance. One study[91] used a relatively lower dose of haloperidol (1–4 mg/d); doses of ziprasidone were consistent across studies. All studies followed patients for >6 months, and one study[122] followed patients for 3.75 years. Risk of bias was high for two studies and unclear for one;[122] all studies declared industry support.

Figure 30. Haloperidol versus ziprasidone – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Health-related Quality of Life

A single trial[91] (n = 185) comparing 1–4 mg/d haloperidol with 40-160 mg/d ziprasidone reported no significant difference between groups for health-related quality of life based on the Manchester Short Assessment of Quality of Life Scale. The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded. Another trial[122] (n = 599) compared 5–20 mg/d haloperidol with 80–160 mg/d ziprasidone and found a significant difference favoring ziprasidone on the Quality of Life Scale (Table 46). This trial included a mix of patients with respect to disorder subtype, comorbid drug

or alcohol use, and treatment resistance. Duration of followup was 3.75 years. The trial had unclear risk of bias and was industry-funded.

Key Question 5. Subgroups

None of the included studies addressed the prespecified subgroups for the key core illness symptoms.

Table 46. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Negative Symptoms					
PANSS[86,122]	2	900	0.56 (-0.30, 1.42)	0%	ND
General Psychopathology					
CDS–S[91]	1	185	0.00 (-0.71, 0.71)	NE	ND
Covi anxiety[57]	1	567	0.63 (-1.23, 2.49)	NE	ND
MADRS[86]	1	301	0.10 (-1.85, 2.05)	NE	ND
Global Ratings and Total Scores					
BPRS[57,73,83,86]	4	1078	0.24 (-0.57, 1.06)	0%	ND
CGI–S[57,83,86,91]	4	1143	-0.00 (-0.26, 0.26)	28%	ND
GAF[86,91,122]	3	1085	0.30 (-1.58, 2.19)	0%	ND
PANSS[69,86,91,122]	4	1105	1.22 (-0.62, 3.07)	0%	ND
Sexual Dysfunction					
Sexual dysfunction (UKU)[91]	1	185	0.69 (0.45, 1.07)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/re–hospitalization[86,91]	2	486	2.62 (0.99, 6.97)*	0%	ND
Other Outcomes					
Response rates[57,69,73,83,86,91]	6	1283	0.98 (0.74, 1.30)*	80%	ND
Remission rates[86,91,122]	3	1085	0.89 (0.71, 1.12)*	12%	ND
Health-Related Quality of Life					
MANSA scale[91]	1	185	-0.10 (-1.48, 1.28)	NE	ND
QLS[122]	1	599	**-12.12 (-22.06, -2.17)**	NE	ziprasidone

BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; I^2 = I-squared; MADRS = Montgomery-Asberg Depression Scale; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life scale; UKU = Udvalg for Kliniske Undersogelser
Note: bold = statistically significant.
*Binary outcome.

Table 47. Strength of evidence (GRADE): haloperidol versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Negative Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
General Psychopathology						
CDS–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Covi nxiety	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
MADRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI–S	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
GAF	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; I^2 = I-squared; MADRS = Montgomery-Asberg Depression Scale; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence

Perphenazine Versus Aripiprazole

One RCT[93] (n = 300) compared perphenazine (8–64 mg/d) with aripiprazole (15–30 mg/d) in patients with **treatment-resistant schizophrenia** (Table 48). There were no significant differences in **core illness symptoms** (global ratings/total scores) or **response rates** (Table 49). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 50). A significant difference favoring perphenazine was reported showing a 20 percent improvement for **health-related quality of life**.

Table 48. Characteristics of RCT comparing perphenazine versus aripiprazole in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2007[93] RCT (6 wks)	G1: PER (8–64mg/d); (146) G2: ARI (15–30mg/d); (154) Washout period: 2–14 d Run–in phase: 4–6 wks	Tx resistant Sz with OLA or RIS; no schizoaffective disorder, residual schizophrenia, BP, refractory response to prior CLO or PER	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP = bipolar disorder; CLO = clozapine; D = day; G = group; Mg = milligrams; No. = number; OLA = olanzapine; PER = perphenazine; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s)

Table 49. Evidence summary table: perphenazine versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Global Ratings and Total Scores					
CGI–I[93]	1	300	-0.20 (-0.52, 0.12)	NE	ND
CGI–S[93]	1	300	0.00 (-0.25, 0.25)	NE	ND
PANSS scale[93]	1	300	-0.70 (-5.61,4.21)	NE	ND
PANSS–derived BPRS[93]	1	300	0.00 (-0.99,0.99)	NE	ND
Other Outcomes					
Response rates[93]	1	300	0.95 (0.64, 1.40)*	NE	ND
Health-Related Quality of Life					
Health-related quality of life (20% improvement)[93]	1	300	4.74 (2.58, 8.69)	NE	perphenazine

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; I2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 50. Strength of evidence (GRADE): perphenazine versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings and Total Scores						
CGI–I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS–derived BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Olanzapine

Two RCTs[23,131] (n = 874) compared perphenazine with olanzapine. Key characteristics of the included trials and summary findings are presented in Table 51 and Table 52. Publication bias

was not formally tested due to the inclusion of a small number of trials. The SoE for all evaluated outcomes was insufficient due to the inclusion of only two trials (Table 53).

Table 51. Characteristics of RCTs comparing perphenazine versus olanzapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Ascher-Svanum et al. 2008[131] RCT (1 yr)	G1: PER (NR); (48) G2: OLA (NR); (229)	Sz, schizoaffective or schizophreniform disorders; BPRS ≥18	Unclear, Industry
Lieberman et al. 2005[23] RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: OLA (7.5–30mg/d); (336)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

BPRS = Brief Psychiatric Rating Scale; D = day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); No. = number; NR = not reported; OLA = olanzapine; PER = perphenazine; RCT = randomized controlled trial; Sz = schizophrenia; Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

One trial[23] (n = 597) including patients with schizophrenia compared perphenazine (8–32 mg/d) and olanzapine (7.5–30 mg/d) and reported on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI–S scales. All the findings significantly favored olanzapine, except PANSS (total), which favored perphenazine, and PANSS (negative), which was not significantly different between groups (Table 52). The differences were not considered to be clinically relevant, and the SoE for all outcomes was graded as insufficient (Table 53).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Employment or Personal Earnings

One trial[23] (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the employment or personal earnings (Table 52).

Health Care System Utilization

One trial[23] (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the rates of hospitalization or rehospitalization (Table 52).

Other Outcomes

One trial[23] (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the Quality of Life Scale (total score) (Table 52). One trial[131] of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder reported a significantly longer time to all-cause medication discontinuation (days) favoring olanzapine (Table 52).

Key Question 5. Subgroups

Comorbidities

One trial[23] (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported on a subgroup of patients with comorbid illicit substance use. There was a significant difference in favor of olanzapine on PANSS (positive) (MD = 1.91; 95% CI, 0.57 to 3.25), PANSS (negative) (MD = 1.67; 95% CI, 0.17 to 3.17), and CGI–S (MD = 0.43; 95% CI, 0.17 to 0.69). There was a significant difference in favor of perphenazine for PANSS (total) (MD = -5.11; 95% CI, -9.31 to -0.91). No difference between groups was found for the PANSS (general psychopathology). The differences were not considered to be clinically relevant.

Table 52. Evidence summary table: perphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[23]	1	597	1.47 (0.55, 2.40)	NE	olanzapine
Negative Symptoms					
PANSS[23]	1	597	0.43 (-0.55, 1.41)	NE	ND
General Psychopathology					
PANSS[23]	1	597	2.17 (0.66, 3.68)	NE	olanzapine
Global Ratings and Total Scores					
CGI–S[23]	1	597	0.25 (0.06, 0.43)	NE	olanzapine
PANSS[23]	1	597	-4.59 (-7.42, -1.77)	NE	perphenazine
Employment/ Personal Earnings					
Paid employment in past month[23]	1	597	1.29 (0.70, 2.38)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[23]	1	597	1.39 (0.92, 2.09)*	NE	ND
Health-Related Quality of Life					
QLS Total score[23]	1	597	0.00 (-0.16, 0.16)	NE	ND
Medication Adherence					
Time to all-cause medication discontinuation (days)[131]	1	277	-78.70 (-119.34, -38.06)	NE	olanzapine

Note: bold = statistically significant; * = binary outcome; CGI–S = Clinical Global Impression–Severity; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

Table 53. Strength of evidence (GRADE): perphenazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI–S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI–S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Quetiapine

One RCT[23] (n = 598) compared perphenazine (8–32 mg/d) with quetiapine (200–800 mg/d) in patients with schizophrenia (Table 54). No significant differences between groups were found for **core illness symptoms** (positive or negative symptoms, general psychopathology, or total scores), **functional outcomes** (paid employment in past month), **health care system utilization**, or **quality of life scores** (Table 55). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 56). For **subgroup** analysis investigating comorbidities, no significant differences were found between groups on PANSS (positive, negative, general psychopathology, or total score) or CGI–S.

Table 54. Characteristics of RCT comparing perphenazine versus quetiapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Lieberman et al. 2005[23] RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: QUE (200–800mg/d); (337)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

D = day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); PER = perphenazine; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia

Table 55. Evidence summary table: perphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[23]	1	586	-0.93 (-1.93, 0.06)	NE	ND
Negative Symptoms					
PANSS[23]	1	586	-0.70 (-1.66, 0.26)	NE	ND
General Psychopathology					
PANSS[23]	1	586	-0.54 (-2.10, 1.02)	NE	ND
Global ratings and Total Scores					
CGI[23]	1	586	-0.17(-0.36, 0.01)	NE	ND
PANSS[23]	1	586	1.52 (-1.39, 4.43)	NE	ND
Employment/ Personal Earnings					
Paid employment in past month[23]	1	598	1.75 (0.90, 3.43)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[23]	1	598	0.78 (0.55, 1.11)*	NE	ND
Health-related Quality of Life					
Quality of Life Scale Total score[23]	1	598	0.10 (-0.07, 0.27)	NE	ND

* = binary outcome; CGI = Clinical Global Impression; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 56. Strength of evidence (GRADE): perphenazine versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Risperidone

Two RCTs[23,131] (n = 871) in patients with schizophrenia compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d). Key characteristics of the included trials and summary findings are presented in Table 57 and Table 58. Publication bias was not formally tested due to the inclusion of a small number of trials. The SoE for all evaluated outcomes was insufficient due to the inclusion of only a small number of trials (Table 59).

Table 57. Characteristics of RCTs comparing perphenazine versus risperidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Ascher-Svanum et al. 2008[131] RCT (1 yr)	G1: PER (NR); (48) G2: RIS (NR); (221)	Sz, schizoaffective or schizophreniform disorders; BPRS >18	Unclear, Industry
Lieberman et al. 2005[23] RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: RIS (1.5–6.0mg/d); (341)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

BPRS = Brief Psychiatric Rating Scale; D = day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); NR = not reported; PER = perphenazine; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

One trial[23] (n = 602) including patients with schizophrenia and comparing perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI–S (Table 58). The SoE for the outcomes was graded as insufficient (Table 59).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Employment or Personal Earnings

One trial[23] (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups for the employment or personal earnings (Table 58).

Health Care System Utilization

One trial[23] (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on rates of hospitalization or rehospitalization (Table 58).

Other Outcomes

One trial[23] (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on the Quality of Life Scale (total score) (Table 58). Another trial[131] in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder reported no significant difference between groups for all-cause medication discontinuation (days) (Table 58).

Key Question 5. Subgroups

Comorbidities

One trial,[23] including patients with schizophrenia and comparing perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d), reported on a subgroup of patients with comorbid illicit substance use. There was no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), or CGI–S.

Table 58. Evidence summary table: perphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[23]	1	590	-0.06 (-1.04, 0.94)	NE	ND
Negative Symptoms					
PANSS[23]	1	590	-0.87 (-1.86, 0.12)	NE	ND
General Psychopathology					
PANSS[23]	1	590	0.24 (-1.39, 1.87)	NE	ND
Global Ratings and Total Scores					
CGI[23]	1	590	-0.06 (-0.25, 0.13)	NE	ND
PANSS[23]	1	590	0.17 (-2.84, 3.22)	NE	ND
Employment/ Personal Earnings					
Paid employment in past month[23]	1	602	1.38 (0.74, 2.57)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization[23]	1	602	1.05 (0.72, 1.53)*	NE	ND
Health-Related Quality of Life					
Quality of Life Scale Total score[23]	1	602	-0.07 (-0.24, 0.10)	NE	ND
Medication Adherence					
Time to all-cause medication discontinuation (days)[131]	1	269	-33.40 (-75.18, 8.38)	NE	ND

CGI = Clinical Global Impression; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

*Binary outcome.

Table 59. Strength of evidence (GRADE): perphenazine versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Ziprasidone

One RCT[23] (n = 446) compared perphenazine (8–32 mg/d) with ziprasidone (40–160 mg/d) in patients with schizophrenia (Table 60). No significant differences were found between groups for **core illness symptoms** (positive, negative, and total scores); however, a significant difference favoring perphenaine for **core illness symptoms** (general psychopathology) was found, but was considered not clinically significant (Table 61). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 62). No significant differences were found between groups for **functional outcomes** (paid employment in past month), **health care system utilization** (rates of hospitalization or rehospitalisation), **quality of life scores**, or for subgroup analysis investigating **comorbid** illicit substance use.

Table 60. Characteristics of RCT comparing perphenazine versus ziprasidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Lieberman et al. 2005[23] RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: ZIP (40–160mg/d); (185)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

d = Day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); PER = perphenazine; RCT = randomized controlled trial; Sz = schizophrenia; ZIP = ziprasidone

Table 61. Evidence summary table: perphenazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Positive Symptoms					
PANSS[23]	1	440	-0.85 (-2.06, 0.35)	NE	ND
Negative Symptoms					
PANSS[23]	1	440	-0.97 (-2.05, 0.11)	NE	ND
General Psychopathology					
PANSS[23]	1	440	-1.92 (-3.71, -0.14)	NE	perphenazine
Global Ratings and Total Scores					
CGI[23]	1	440	-0.12 (-0.34, 0.10)	NE	ND
PANSS[23]	1	440	2.23 (-1.18, 5.63)	NE	ND
Employment or Personal Earnings					
Paid employment in past month[23]	1	446	1.22 (0.60, 2.51)*	NE	ND

Table 61. Evidence summary table: perphenazine versus ziprasidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Health Care System Utilization					
Rates of hospitalization or rehospitalization[23]	1	446	0.88 (0.58, 1.34)*	NE	ND
Health-Related Quality of Life					
Quality of Life Scale Total score[23]	1	446	-0.07 (-0.27, 0.13)	NE	ND

Note: bold = statistically significant; * = point estimate reflex relative risk; CGI = Clinical Global Impression; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

Table 62. Strength of evidence (GRADE): perphenazine versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Trifluoperazine Versus Clozapine

One RCT[157] (n = 25) compared trifluoperazine (7.5–15 mg/d) with clozapine (50–100 mg/d) in patients schizophrenia (Table 63). There was no reported difference in core illness symptoms (BPRS) (Table 64). No other relevant outcomes were reported. The SoE for BPRS was insufficient (Table 65).

Table 63. Characteristics of RCTs comparing trifluoperazine versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Rinieris et al. 1980[157] RCT (6 wks)	G1: TRI (7.5–15mg/d); (20) G2: CLO (50–100mg/d); (5) Run-in phase: 1 wk	Sz not further defined	High, NR

CLO = clozapine; D = days; G = group; Mg = milligrams; No. = number; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; TRI = Trifluoperazine; Wk(s) = week(s)

Table 64. Evidence summary table: trifluoperazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Global Ratings					
BPRS[157]	1	25	2.50 (-4.19, 9.19)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I^2 = I-squared; ND = no difference; NE = not estimable

Table 65. Strength of evidence (GRADE): trifluoperazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Bipolar Disorder (Key Questions 1, 2, 4, 5)

For bipolar disorder, we included 11 trials that enrolled a total of 2,217 adult patients. The individual studies are described in Appendix H and I. The results from the studies and pooled analyses are presented in Table 66 to Table 82. Within the forest plots, the studies are presented by year of publication. The following sections provide an overview of results according to KQ: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For KQ1, the outcomes are grouped as follows: mood (mania), mood (depression), positive and negative symptoms, general psychopathology, and global ratings and total scores. KQs 2 and 4 were grouped and are reported together throughout the results section. Comparisons are presented in alphabetic order by drug name.

Chlorpromazine Versus Clozapine

One RCT[48] (n = 27) compared chlorpromazine (2–5 mg/d) with clozapine (25–175 mg/d) in patients with bipolar disorder and manic episodes (Table 66). No significant differences were found between groups for **mood (mania)** (YMRS scale) (Table 67). The SoE was insufficient due to the inclusion of only a single trial (Table 68). Other reported AEs were not different between groups (Appendix N, Tables 113 and 114).

Table 66. Characteristics of RCT comparing chlorpromazine versus clozapine in the treatment of bipolar disorder with manic episodes

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Barbini et al. 1997[48] RCT (3 wks)	G1: CHL (2–5mg/kg/d); (12) G2: CLO (25–175mg/d); (15)	BP with manic episode; no depot AP <6 mo	High, NR

AP(s) = antipsychotic(s); BP = bipolar disorder; CHL = chlorpromazine; CLO = clozapine; D = days; G = group; Kg = kikograms; Mg = milligrams; Mo = month; NR = not reported; RCT = randomized controlled trial; Wk(s) = week(s);

Table 67. Evidence summary table: chlorpromazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Mood (Mania)					
YMRS scale[48]	1	27	3.94 (-0.11, 7.99)	NE	ND

I^2 = I-squared; ND = no difference; NE = not estimable; YMRS = Young Mania Rating Scale

Table 68. Strength of evidence (GRADE): chlorpromazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Aripiprazole

Two RCTs[32,33] (n = 679) compared haloperidol with aripiprazole. Key characteristics of the included trials and findings are summarized in Table 69 and Table 70. Both studies included only patients with bipolar I disorder and no comorbid drug or alcohol use. Young et al.[33] only included patients with multiple episodes and no treatment resistance, whereas Vieta et al.[32] had no restrictions regarding first versus multiple episodes or treatment resistance. Doses were the same for both studies: 10–15 mg/d haloperidol and 15–30 mg/d aripiprazole. Duration of followup was 12 weeks in both studies. Both trials had unclear risk of bias was and were industry-funded.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the evaluated outcomes was low or insufficient due to the small number of included trials (Table 71).

Table 69. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Vieta et al. 2005[32] RCT (12 wks)	G1: HAL (10–15mg/d); (172) G2: ARI (15–30mg/d); (175) Washout period: 1–3 d	BP; no rapid-cycling BP I, current manic episode >4 wks, substance abuse, or unresponsive to previous AP	Unclear, Industry
Young et al. 2009[33] RCT (12 wks)	G1: HAL (5–15mg/d); (165) G2: ARI (15–30mg/d); (167) Washout period: 2–14 d	BP I manic or mixed type (with or without psychotic features)	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP I = bipolar disorder type I; D = days; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; RCT = randomized controlled trial; Wk(s) = week(s)

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

Two trials[32,33] (n = 679) assessed global ratings and total scores based on the YMRS; however, there was moderate heterogeneity for the YMRS. The study characteristics are described above which may explain some of the heterogeneity observed in effect estimates. Nevertheless, none of the studies individually showed significant effects. The SoE was graded as low for YMRS (Table 71).

Mood: Depression

Pooled results from the two included trials[32,33] (n = 679) showed no significant difference in total scores based on the MADRS (Table 70); however, statistical heterogeneity was substantial across studies. The SoE was graded as low (Table 71).

Positive and Negative Symptoms

Young et al.[33] (n = 332) found no significant difference in positive symptoms based on the PANSS (positive) or negative symptoms on the PANSS (negative) (Table 70). The SoE was graded as insufficient for both scales (Table 71).

Global Ratings and Total Scores

Two trials[32,33] (n = 679) assessed global ratings on the Clinical Global Impression–Bipolar (CGI–BP) version, with one study[33] also assessing PANSS (total) (Table 70). No significant differences were found on either scale; however there was substantial heterogeneity for the CGI–BP. The study characteristics are described above which may explain some of the heterogeneity observed in effect estimates. Nevertheless, none of the studies individually showed significant effects. The SoE was graded as low for CGI–BP and insufficient for PANSS (total) (Table 71).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Other Outcomes. The two relevant trials[32,33] reported no significant difference in response rates overall; however, statistical heterogeneity was substantial (Table 70). Vieta et al.[32] had no

restrictions regarding first versus multiple episodes or treatment resistance and showed a significant difference favoring haloperidol. In contrast, Young et al.[33] only included patients with multiple episodes and no treatment resistance and showed no difference between groups.

Vieta et al.[32] (n = 347) found a significant difference in relapse rates favoring haloperidol (Table 70). Young et al.[33] (n = 332) found no significant difference in remission rates (Table 70).

Key Question 5. Subgroups

Neither study addressed the prespecified subgroups.

Table 70. Evidence summary table: haloperidol versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Mood (Mania)					
YMRS[32,33]	2	679	0.90 (-0.77, 2.58)	22%	ND
Mood (Depression)					
MADRS[32,33]	2	679	0.22 (-1.73, 2.18)	0%	ND
Positive/Negative Symptoms					
PANSS (positive)[33]	1	332	-0.50 (-1.61, 0.61)	NE	ND
PANSS (negative)[33]	1	332	-0.10 (-0.65, 0.45)	NE	ND
Global Ratings and Total Scores					
CGI–BP[32,33]	2	679	0.15 (-0.35, 0.65)	81%	ND
PANSS[33]	1	332	-1.90 (-4.95, 1.15)	NE	ND
Other Outcomes					
Relapse rates[32]	1	347	0.53 (0.40, 0.71)*	NE	haloperidol
Remission rates[33]	1	332	1.02 (0.89, 1.17)*	NE	ND
Response rates[32,33]	2	679	0.77 (0.42, 1.42)*	94%	ND

Note: bolded results are statistically significant; * = binary outcome; CGI–BP = Clinical Global Impression–Bipolar; I^2 = I-squared; MADRS = Montgomery-Asberg Depression Rating; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale

Table 71. Strength of evidence (GRADE): haloperidol versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
MADRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Positive/Negative Symptoms						
PANSS (positive)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS (negative)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI–BP	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS (total)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI–BP = Clinical Global Impression–Bipolar; MADRS = Montgomery-Asberg Depression Rating; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence; Total = total scores; YMRS = Young Mania Rating Scale; ND = no difference

Haloperidol Versus Olanzapine

Two trials[119,140] (n = 463) compared haloperidol with olanzapine. Key trial characteristics and findings are summarized in Table 72 and Table 73. Moreno et al.[119] included only patients with bipolar II disorder, whereas Tohen et al.[140] included only patients with bipolar I disorder. Both studies included only patients with no comorbid drug or alcohol use and included mixed

populations with respect to first versus multiple episodes and treatment resistance. Drug doses were consistent across studies: 3–15 mg/d haloperidol versus 5–20 mg/d olanzapine.

Moreno et al.[119] and Tohen et al.[140] followed patients for 6 and 12 weeks, respectively. Moreno et al.[119] had unclear risk of bias and was supported through foundation funding; Tohen et al.[140] had high risk of bias and was industry-funded.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for all the evaluated outcomes was insufficient due to the small number of included trials (Table 74).

Table 72. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion criteria	Risk of Bias, Financial Support
Moreno et al. 2007[119] RCT (6 wks)	G1: HAL (3–15mg/d); (5) G2: OLA (5–20mg/d); (7) Washout period: 4 d	BP; switched between depression and mania phase ≤1 mo before or after PSG procedure	Unclear, Foundation
Tohen et al. 2003[140] RCT (12 wks)	G1: HAL (3–15mg/d); (219) G2: OLA (5–20mg/d); (234)	BP defined by DSM–IV	High, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; OLA = olanzapine; PSG = polysomnographic studies; RCT = randomized controlled trial; Wk(s) = week(s);

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

Both trials[119,140] (n = 465) assessed total score using YMRS and found no differences between groups; results were statistically homogeneous across studies (Table 73). The SoE for YMRS was graded as low.

Mood: Depression

Tohen et al.[140] (n = 453) found no significant differences based on HAM–D (Table 73). The SoE was graded as insufficient (Table 74).

Sleep

Moreno et al.[119] (n = 12) found no significant differences in number of awakenings, sleep efficiency, stage rapid eye movement, total rapid eye movement, or total sleep time (Table 73). The SoE was graded as insufficient (Table 74).

Global Ratings and Total Scores

Moreno et al.[119] (n = 12) assessed total score with CGI–BP and showed no difference between groups. The SoE for CGI–BP was graded as insufficient (Table 74).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Tohen et al.[140] (n = 453) examined patients with bipolar I and found a significant difference on the number of days worked for pay favoring olanzapine, but not for the Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Followup Evaluation household or work activities impairment scores (Table 73).

Other Outcomes

Tohen et al.[140] (n = 453) reported on relapse, response, and remission rates; no significant difference was found between groups for any of the outcomes (Table 73). The same trial[140] assessed health-related quality of life using the Short Form–36 (Table 73). Results showed a significant difference on the mental summary score favoring haloperidol and a significant difference on the physical summary score favoring olanzapine (Table 73).

Key Question 5. Subgroups

Disorder Subtype

Tohen et al.[140] included only patients with bipolar I disorder and found no significant difference on HAM–D or YMRS.

Moreno et al.[119] included only patients with bipolar II disorder and found no significant difference on number of awakenings, sleep efficiency, rapid eye movement, rapid eye movement activity, total sleep time (minutes), the CGI–BP, or the YMRS.

Table 73. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Mood (Mania)					
YMRS[119,140]	2	465	-0.37 (-1.98, 1.24)	0%	ND
Mood (Depression)					
HAM–D[140]	1	453	0.90 (-0.64, 2.44)	NE	ND
Sleep					
Number of awakenings[119]	1	12	11.40 (-10.44, 33.24)	NE	ND
Sleep efficiency (%)[119]	1	12	-8.90 (-34.65, 16.85)	NE	ND
Stage REM (min)[119]	1	12	-10.70 (-54.10, 32.70)	NE	ND
Total REM activity[119]	1	12	-29.30 (-85.88, 27.28)	NE	ND
Total sleep time (min)[119]	1	12	18.60 (-107.21,144.41)	NE	ND
Global Ratings and Total Scores					
CGI–BP[119]	1	12	-1.80 (-5.66, 2.06)	NE	ND
Employment/ Personal Earnings					
Active workers: number working for pay[140]	1	453	0.50 (0.32, 0.79)*	NE	olanzapine
SLICE/LIFE: household activities impairment score[140]	1	453	0.23 (-0.10, 0.56)	NE	ND
SLICE/LIFE: work activities impairment score[140]	1	453	0.00 (-0.33, 0.33)	NE	ND

Table 73. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Relapse rates[140]	1	453	0.80 (0.52, 1.24)*	NE	ND
Remission rates[140]	1	453	0.85 (0.70, 1.03)*	NE	ND
Response rates[140]	1	453	0.98 (0.94, 1.02)*	NE	ND
Health-Related Quality of Life					
SF–36 mental summary score[140]	1	453	17.30 (14.47, 20.13)	NE	haloperidol
SF–36 physical summary score[140]	1	453	-3.74 (-5.46, -2.02)	NE	olanzapine

Note: bolded results are statistically significant; * = binary outcome; CGI–BP = Clinical Global Impression–Bipolar; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; ND = no difference; NE = not estimable; REM = rapid eye movement; SF = Short Form; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Followup Evaluation; YMRS = Young Mania Rating Scale

Table 74. Strength of evidence (GRADE): haloperidol versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
HAM–D	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Sleep						
Number of awakenings	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Sleep efficiency (%)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Stage REM (min)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Total REM activity	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Total sleep time (min)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI–BP	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI–BP = Clinical Global Impression–Bipolar; HAM–D = Hamilton Rating Scale for Depression; Min = minute; ND = no difference; RCT = randomized controlled trial; REM = rapid eye movement; RoB = risk of bias; SoE = Strength of Evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Quetiapine

One trial[115] (n = 201) compared haloperidol (2–8 mg/d) with quetiapine (100–800 mg/d) in patients with bipolar disorder in a current manic episode with or without psychotic features (Table 75). This trial did not report **core illness symptoms**, or investigate **subgroups** (Table 76). No significant differences between groups were found for response rates or remission rates.

Table 75. Characteristics of RCT comparing haloperidol versus quetiapine in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
McIntyre et al. 2005[115] RCT (12 wks)	G1: HAL (2–8mg/d); (99) G2: QUE (100–800mg/d); (102)	BP I, current episode manic, with or without psychotic features; ≥1 manic or mixed episode; no tx with CLO ≤1 mo	Unclear, Industry

BP I = bipolar disorder type I; CLO = clozapine; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; QUE = quetiapine; RCT = randomized controlled trial; Wk(s) = week(s);

Table 76. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Other Outcomes					
Remission rates[115]	1	201	1.14 (0.94, 1.40)*	NE	ND
Response rates[115]	1	201	1.03 (0.83, 1.28)*	NE	ND

I^2 = I-squared; ND = no difference; NE = not estimable
*Binary outcome.

Haloperidol Versus Risperidone

Key Points:

- Four RCTs compared haloperidol with risperidone; three of the studies included both bipolar I and bipolar II patients, whereas one trial included only bipolar I disorder.
- The most commonly reported outcome was mood (mania) using the YMRS. Pooled results from three studies showed no differences between groups. The SoE was low.
- Other outcomes were assessed in single studies and no significant differences were reported.

Four trials[90,128,133,138] involving 463 adults with bipolar disorder compared haloperidol with risperidone. Key characteristics of the included trials and summary findings are presented in Table 77 and Table 78. Three studies included mixed bipolar I and bipolar II disorder, whereas one study[138] included only patients with bipolar I disorder. All studies restricted inclusion to patients with no comorbid drug or alcohol use. Two studies[128,138] only included patients with multiple episodes; two studies[90,133] included both patients with first and multiple episodes. One study[138] specifically excluded patients with treatment resistance. Dosages for haloperidol ranged from 4–20 mg/d and for risperidone ranged from 2–10 mg/d.

Duration of followup was ≤6 weeks in three studies[90,128,133] and 12 weeks in the fourth.[138] Risk of bias was high for two studies[90,128] and unclear for two studies.[133,138] All studies were funded by industry.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for all the evaluated outcomes was insufficient or low due to the small number of included trials (Table 79).

Table 77. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Janicak et al. 2001[90] RCT (6 wks)	G1: HAL (4–20mg); (32) G2: RIS (2–10mg); (30) Washout period: ~5 d	BP subtype, manic phase; no hypersensitivity hx to HAL or RIS	High, Industry
Sachs et al. 2002[128] RCT (3 wks)	G1: HAL (4–12mg/d); (53) G2: RIS (2–6mg/d); (52) Washout period: ≤3 d	BP and ≥1 prior manic episode; no CLO ≤1 month or depot AP within one cycle	High, Industry
Segal et al. 1998[133] RCT (28 d)	G1: HAL (10mg/d); (15) G2: RIS (6mg/d); (15)	BP with acute manic episode defined by DSM-IV	Unclear, Industry
Smulevich et al. 2005[138] RCT (12 wks)	G1: HAL (4–12mg/d); (144) G2: RIS (2–6mg/d); (154) Washout period: ≥3 d	BP I with ≥1 manic or mixed episode; no schizoaffective disorder, rapid-cycling BP, borderline or antisocial personality disorders	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; CLO = clozapine; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; No = number; NR = not reported; RIS = risperidone; RCT = randomized controlled trial; Wk(s) = week(s)

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

All four trials[90,128,133,138] presented results for mood (mania) using two scales. One trial[90] (n = 62) assessed mania symptoms using the Clinician-Administered Rating Scale for Mania; no differences between groups were found. The study compared 4–20 mg/d haloperidol with 2–10 mg/d risperidone. The trial included mixed populations with respect to type of bipolar disorder (I and II), first and previous episodes, and treatment resistance. Patients with comorbid drug or alcohol use were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Three trials[128,133,138] (n = 433) showed no differences based on the YMRS; the pooled results showed no statistical heterogeneity. Two of the studies included patients with both bipolar I and II disorders, whereas the third study[138] included only bipolar I disorder. Two studies[128,138] included only patients with multiple episodes. One study[138] included patients with no treatment resistance. None of the studies included patients with comorbid drug or alcohol use. Dose ranged from 4–20mg/d for haloperidol and 2–6mg/d for risperidone. Duration of followup ranged from 3 weeks[128] to 12 weeks.[138] Risk of bias was high in one study[128] and unclear in two studies;[133,138] all studies were industry-funded.

Mood: Depression

One trial[90] as above assessed depressive symptoms using the HAM–D; no differences between groups were found.

Positive and Negative Symptoms

One trial[90] described above assessed positive and negative symptoms. No significant difference was found using the PANSS.

Global Ratings and Total Scores

Two trials[90,133] presented results for global ratings and total symptom scores using two scales. One trial[133] (n = 30) comparing 10 mg/d haloperidol with 6 mg/d risperidone reported BPRS and found no difference between groups. The study included patients with both bipolar I and II disorders and excluded patients with comorbid alcohol or drug use. The study population was mixed with respect to first and previous episodes as well as treatment resistance. Duration of followup was 12 weeks. Risk of bias was unclear, and the trial was industry-funded.

One trial[90] comparing 4–20 mg/d haloperidol with 2–10 mg/d risperidone found no differences on the CGI–I or PANSS (total) scale. This trial included mixed populations with respect to type of bipolar disorder (I and II), first and previous episodes, and treatment resistance. The trial excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Other Outcomes

One trial[90] comparing 4–20 mg/d haloperidol with 2–10 mg/d risperidone assessed response rates and and found no difference between groups. This trial included mixed populations with respect to type of disorder (bipolar I and II), first and previous episodes, and treatment resistance. Patients with comorbid drug or alcohol use were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Key Question 5. Subgroups

Disorder Subtype. One trial[138] in 298 patients with bipolar disorder with acute mania compared haloperidol (4–12 mg/d) with risperidone (2–6 mg/d) and found no significant difference on the YMRS.

Table 78. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Mood (Mania)					
CARS-M[90]	1	62	3.00 (-3.36, 9.36)	NE	ND
YMRS[128,133,138]	3	433	1.08 (-0.95, 3.12)	0%	ND
Mood (Depression)					
HAM-D[90]	1	62	-5.00 (-10.86, 0.86)	NE	ND
Positive Symptoms					
PANSS[90]	1	62	-80 (-3.90, 2.30)	NE	ND
Negative Symptoms					
PANSS[90]	1	62	-1.30 (-4.33, 1.73)	NE	ND
Global Ratings and Total Scores					
BPRS[133]	1	30	-1.60 (-7.11, 3.91)	NE	ND
CGI-I[90]	1	62	0.00 (-0.42, 0.42)	NE	ND
PANSS[90]	1	62	-2.00 (-13.10, 9.10)	NE	ND
Other Outcomes					
Response rates[90]	1	62	1.07 (0.44, 2.59)	NE	ND

BPRS = Brief Psychiatric Rating Scale; CARS–M = Clinician-Administered Rating Scale for Mania; CGI–I = Clinical Global Impression–Improvement; HAM–D = Hamilton Rating Scale for Depression; I^2 = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale

Table 79. Strength of evidence (GRADE): haloperidol versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
CARS-M	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
YMRS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
HAM-D	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CARS–M = Clinician-Administered Rating Scale for Mania; CGI–I = Clinical Global Impression–Improvement; HAM–D = Hamilton Rating Scale for Depression; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Ziprasidone

One trial[144] (n = 350) compared haloperidol (8–30 mg/d) with ziprasidone (80–160 mg/d) in patients with bipolar I disorder and mixed or manic subtypes (Table 80). A significant difference favoring haloperidol was found for the improvement of **core illness symptoms**, **response rates**, and for **subgroup analysis** of disorder subtype (Table 81). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 82). No difference between groups was found for **remission rates**.

Table 80. Characteristics of RCT comparing haloperidol versus ziprasidone in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Vieta et al. 2010[144] RCT (12 wks)	G1: HAL (8–30mg/d); (78) G2: ZIP (80–160mg/d); (73) Washout period: 2–10 d	BP I disorder, most recent episode manic or mixed	High, Industry

BP = bipolar; D = days; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; RCT = randomized controlled trial; Wk(s) = week(s); ZIP = ziprasidone

Table 81. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2	Favors
Mood (Mania)					
YMRS[144]	1	350	-5.52 (-7.79, -3.25)	NE	haloperidol
Other Outcomes					
Remission rates[144]	1	350	1.42 (1.00, 2.02)*	NE	ND
Response rates[144]	1	350	1.09 (1.02, 1.16)*	NE	haloperidol

Note: bolded results are statistically significant; * = binary outcome; I^2 = I-squared; ND = no difference; NE = not estimable; YMRS = Young Mania Rating Scale

Table 82. Strength of evidence (GRADE): haloperidol versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Adverse Events (Key Question 3)

This section reviews the evidence on the comparative harms of individual FGAs and SGAs. The results are organized in alphabetical order by drug comparison (Appendix N). For each comparison, we report data on general and specific AEs. We categorized the outcomes by systems. As detailed in the methods section, we extracted only binary data for AEs (i.e., the number of patients who experienced a given event in each group), not continuous data (e.g., mean change in laboratory values). In addition, we counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an AE.

A priori, we identified four AEs to be the most clinically important: diabetes mellitus, tardive dyskinesia, metabolic syndrome, and mortality. Table 83 summarizes the results of studies that provided data for these AEs and the SoE for each comparison. For metabolic syndrome, two RCTs comparing haloperidol with olanzapine found no difference in incidence of metabolic syndrome (low SoE). For mortality, two RCTs comparing chlorpromazine with clozapine and two RCTs comparing haloperidol with aripiprazole showed no difference between the groups (low SoE), although the length of followup of the trials for the latter comparison was only 24 hours. The evidence was insufficient to allow conclusions for the remaining comparisons, primarily because only single studies provided data. The only significant differences in the remaining comparisons showed less incidence with the SGAs with the exception of a higher incidence of patients developing metabolic syndrome with clozapine compared with haloperidol.

Table 83. Summary of the strength of evidence for AEs

Comparison (Number of Studies)	RR (95% CI)	Summary	SoE
Diabetes Mellitus			
Haloperidol vs. olanzapine (1 RCT)	0.85 (0.21 to 3.49)	No significant difference.	Insufficient
Perphenazine vs. olanzapine (1 RCT)	0.81 (0.45 to 1.45)	No significant difference.	Insufficient
Perphenazine vs. quetiapine (1 RCT)	1.57 (0.79 to 3.12)	No significant difference.	Insufficient
Perphenazine vs. risperidone (1 RCT)	1.06 (0.57 to 1.96)	No significant difference.	Insufficient
Perphenazine vs. ziprasidone (1 RCT)	1.00 (0.49 to 2.05)	No significant difference.	Insufficient
Tardive Dyskinesia			
Chlorpromazine vs. clozapine (1 RCT)	3.30 (0.14 to 76.46)	No significant difference.	Insufficient
Chlorpromazine vs. ziprasidone (1 RCT)	1.21 (0.61 to 2.44)	No significant difference.	Insufficient
Haloperidol vs. clozapine (1 cohort)	34.50 (2.07 to 573.55)	Significant difference, with more events for haloperidol.	Insufficient
Haloperidol vs. olanzapine (1 RCT)	11.75 (0.65 to 211.26)	No significant difference.	Insufficient
Haloperidol vs. quetiapine (1 RCT)	NE	Zero events in both groups.	Insufficient
Haloperidol vs. ziprasidone (1 RCT)	4.84 (0.23 to 99.93)	No significant difference.	Insufficient
Metabolic Syndrome			
Haloperidol vs. clozapine (1 RCT)	0.27 (0.10 to 0.75)	Significant difference, with more events for clozapine.	Insufficient
Haloperidol vs. olanzapine (2 RCTs)	0.38 (0.06 to 2.51)	No significant difference.	Low
Perphenazine vs. olanzapine (1 RCT)	0.88 (0.63 to 1.21)	No significant difference.	Insufficient
Perphenazine vs. quetiapine (1 RCT)	1.19 (0.84 to 1.70)	No significant difference.	Insufficient
Perphenazine vs. risperidone (1 RCT)	1.42 (0.98 to 2.06)	No significant difference.	Insufficient
Perphenazine vs. ziprasidone (1 RCT)	1.51 (0.96 to 2.39)	No significant difference.	Insufficient

Table 83. Summary of the strength of evidence for AEs (continued)

Comparison (Number of Studies)	RR (95% CI)	Summary	SoE
Mortality			
Chlorpromazine vs. clozapine (2 RCTs)	0.98 (0.10 to 9.19)	No significant difference.	Low
Chlorpromazine vs. clozapine (1 Cohort)	1.98 (1.30 to 3.00)	Significant difference, with more events for chlorpromazine.	Insufficient
Chlorpromazine vs. ziprasidone (1 RCT)	NE	Zero events in both groups.	Insufficient
Haloperidol vs. aripiprazole (2 RCT)	0.77 (0.04 to 15.91)	No significant difference.	Low
Haloperidol vs. risperidone (1 Cohort)	1.70 (1.31 to 2.20)	Significant difference, with more events for haloperidol.	Insufficient
Thioridazine vs. clozapine (1 Cohort)	2.12 (1.38 to 3.26)	Significant difference, with more events for thioridazine.	Insufficient
Thioridazine vs. risperidone (1 Cohort)	1.82 (1.37 to 2.40)	Significant difference, with more events for thioridazine.	Insufficient

CI = confidence interval; NE = not estimable; RCT = randomized controlled trial; RR = relative risk; SoE = strength of evidence

Chlorpromazine Versus Clozapine

Twelve trials[48,63,87,94,109,152-154,156,158,160,161] reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving clozapine (Table 84).

General Measures

The rates of mortality (2 trials)[109,156] and withdrawals due to AEs (5 trials)[63,87,109,152,160] were not different between groups.

Specific Measures

Behavior and Psychosis

No differences were found in single trials reporting the incidence of agitation,[153] depression,[152] and increasing paranoia and excitement.[154]

Body Mass Index (BMI) and Weight

A single trial[87] reported no differences in incidence of weight gain (>5 percent) and weight loss.

Cardiovascular

Hypertension occurred less frequently with chlorpromazine (2 trials).[94,160] No difference between groups was found for abnormal electrocardiogram (ECG) (2 trials),[154,160] cardiotoxic effects (1 trial),[153] hypotension (5 trials),[48,87,94,109,160] orthostatic hypotension (3 trials),[153,158,160] and tachycardia (2 trials).[87,94]

Cholinergic and Anticholinergic

Dry mouth was reported less frequently with clozapine (5 trials),[63,87,94,152,161] whereas hypersalivation was reported less frequently with chlorpromazine (9 trials).[48,63,87,94,152,154,158,160,161] There was no difference in the incidence of ileus in one trial.[109]

Central Nervous System (CNS)

Drowsiness was less frequent with chlorpromazine (5 trials).[94,152,153,160,161] Dizziness (3 trials),[94,160,161] sedation (3 trials),[48,63,87] seizure (3 trials),[63,87,153] and slurred speech (1 trial)[160] did not differ between groups.

Dermatology

There was no difference between groups in the incidence of dermatologic reactions (3 trials).[87,109,153]

Endocrine (Prolactin and Thyroid)

One trial reported no difference in the incidence hyperprolactinemia.[63]

Extrapyramidal Symptoms or Syndrome (EPS)

EPS were less frequent with clozapine (6 trials).[48,63,87,109,158,160] There was no difference in the incidence of the following AEs: akathisia (3 trials),[63,87,154] dystonia (2 trials),[63,154] oculogyric crisis (1 trial),[154] parkinsonism (2 trials),[153,154] rigidity (3 trials),[63,152,160] staggering (1 trial),[160] deterioration of tardive dyskinesia (1 trial),[87] and tremor (3 trials).[152,160,161]

Genitourinary

In a single trial[63] there was no difference in the incidence of impotence.

Gastrointestinal

No differences were found in the incidence of abdominal cramps (1 trial),[160] constipation (4 trials),[63,94,109,152] diarrhea (1 trial),[160] heartburn (1 trial),[160] and nausea or vomiting (3 trials).[87,94,160]

Hematology

No differences were found in the incidence of agranulocytosis (2 trials),[63,94] abnormal blood cell count (1 trial),[154] neutropenia (1 trial),[109] elevated platelet count (1 trial),[154] and leukocytopenia (4 trials).[48,63,87,94]

Hepatobiliary

No differences in the incidence of elevated hepatic enzymes (2 trials)[87,94] or jaundice (1 trial)[87] were reported.

Sleep

No differences in the incidence of deep sleep or sleep disturbances were reported in a single trial.[153]

Respiratory and Airway

No difference in the incidence of coughing was reported in one trial.[160]

Systemic AEs

Fever or chills were reported less frequently with chlorpromazine (2 trials).[94,160] There were no differences between groups in the incidence of accidental falls (1 trial),[87] headaches (2 trials),[94,160] hyperthermia (3 trials),[109,154,160] and tension (1 trial).[160]

Table 84. Evidence summary table: chlorpromazine versus clozapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Cardiovascular					
Hypertension[94,160]	2	312	0.39 (0.17, 0.90)	0%	chlorpromazine
Cholinergic and Anticholinergic					
Dry mouth[63,87,94,152,161]	5	563	3.00 (1.67, 5.40)	11%	clozapine
Hypersalivation[48,63,87,94,152,154,158,160,161]	9	674	0.25 (0.14, 0.45)	13%	chlorpromazine
CNS					
Drowsiness[94,152,153,160,161]	5	457	0.75 (0.58, 0.97)	0%	chlorpromazine
EPS					
EPS[48,63,87,109,158,160]	6	451	2.75 (1.48, 5.12)	0%	clozapine
Systemic AE					
Fever or chills[94,160]	2	312	0.35 (0.15, 0.83)	0%	chlorpromazine

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; I^2 = I–squared; KQ = Key Question

Chlorpromazine Versus Olanzapine

A single trial[66] reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving olanzapine (Table 85). The incidence of orthostatic hypotension, dry mouth, unsteady gait, and constipation was less frequent with olanzapine. Other reported AEs were not different between groups (Appendix N, Tables 115 and 116).

Table 85. Evidence summary table: chlorpromazine versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Cardiovascular					
Orthostatic hypotension[66]	1	84	7.50 (2.90, 19.42)	NE	olanzapine
Cholinergic and Anticholinergic					
Dry mouth[66]	1	84	1.94 (1.27, 2.97)	NE	olanzapine
CNS					
Unsteady gait[66]	1	84	15.00 (2.07, 108.48)	NE	olanzapine
GI					
Constipation[66]	1	84	2.60 (1.02, 6.65)	NE	olanzapine

AE = adverse event; CNS = Central Nervous System; GI = gastrointestinal; I^2 = I-squared; KQ = Key Question; NE = not estimable

Chlorpromazine Versus Quetiapine

A single trial[121] reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving quetiapine (Table 86). The incidence of orthostatic hypotension was less frequent with quetiapine. Other reported AEs did not differ between groups (Appendix N, Tables 117 and 118).

Table 86. Evidence summary table: chlorpromazine versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Cardiovascular					
Orthostatic hypotension[121]	1	201	3.64 (1.40, 9.42)	NE	quetiapine

AE = adverse event; I^2 = I-squared; KQ = Key Question; NE = not estimable

Chlorpromazine Versus Ziprasidone

A single trial[96] reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving ziprasidone (Table 87). The incidence of orthostatic hypotension was less frequent with chlorpromazine. Other reported AEs did not differ between groups (Appendix N, Tables 119 and 120).

Table 87. Evidence summary table: chlorpromazine versus ziprasidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
BMI and Weight					
Weight loss[96]	1	306	0.19 (0.06, 0.62)	NE	chlorpromazine

AE = adverse event; I^2 = I-squared; KQ = Key Question; NE = not estimable

Fluphenazine Versus Olanzapine

A single trial[89] comparing the incidence of AEs in patients receiving fluphenazine compared with patients receiving olanzapine showed no difference between groups (Appendix N, Tables 121 and 122).

Fluphenazine Versus Quetiapine

A single trial[67] reported on the incidence of AEs in patients receiving fluphenazine compared with patients receiving quetiapine; no difference in reported AEs or persistence and reversibility of AEs were found (Appendix N, Tables 123, 124, and 125).

Fluphenazine Versus Risperidone

A single trial[67] reported on the incidence of AEs in patients receiving fluphenazine compared with patients receiving quetiapine; no difference in reported AEs or persistence and reversibility of AEs were found (Appendix N, Tables 126, 127, and 128).

Haloperidol Versus Aripiprazole

Nine trials[31-33,44,73,74,76,92,98] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving aripiprazole (Table 88). The statistically significant findings are presented in Table 89. Other reported AEs did not differ between groups (Appendix N, Tables 129 and 130).

General Measures

The incidence of patients with AEs (3 trials)[31,73,98] and withdrawals due to AEs (7 trials)[31-33,44,76,92,98] were less frequent with aripiprazole. Rates of mortality (2 trials)[31,44] and serious adverse events (SAEs) (6 trials)[31-33,44,76,92] were not different between groups.

Specific Measures

Behavior and Psychosis

The incidence of mania in a single trial[33] was less frequent with haloperidol. No differences between groups were found for agitation (4 trials),[31,44,74,98] anxiety (4 trials),[33,74,92,98] depression (2 trials),[32,33] clinical deterioration (1 trial),[73] and psychosis (1 trial).[98]

BMI and Weight

No difference between groups was found for weight gain (3 trials).[33,92,98]

Cardiovascular

The incidence of ECG abnormalities (3 trials),[31,32,92] orthostatic hypotension (1 trial),[92] and tachycardia (1 trial)[31] were not different between groups.

CNS

Dizziness (3 trials)[31,44,92] was less frequent with haloperidol, and somnolence (6 trials)[31,33,44,74,92,98] was less frequent with aripiprazole. No difference was reported for the incidence of seizures in a single trial.[31]

Dermatology

Two trials found no difference between groups in injection site reactions.[31,44]

Endocrine (Prolactin and Thyroid)

Hyperprolactinemia (2 trials)[32,33] was less frequent with aripiprazole.

EPS

Akathisia (7 trials),[31-33,74,76,92,98] dystonia (1 trial),[31] EPS (6 trials),[32,33,44,74,92,98] rigidity (1 trial),[33] and tremor (5 trials)[32,33,76,92,98] were less frequent with aripiprazole. No difference was found between groups for asthenia (1 trial)[92] and hypertonia (1 trial).[92]

Gastrointestinal

Dyspepsia (1 trial)[74] was less frequent with aripiprazole; nausea or vomiting (4 trials)[31,44,74,92] was less frequent with haloperidol. There was no difference between groups in the incidence of abdominal pain (1 trial)[92] and diarrhea (1 trial).[74]

Hepatobiliary

A single trial found no difference in the incidence of liver damage.[32]

Ophthalmology

A single trial found the incidence of blurred vision less frequent with aripiprazole.[92]

Sleep

There was no difference between groups in the incidence of insomnia (7 trials).[32,33,44,74,76,92,98]

Systemic AEs

There was no difference in the incidence of headache (7 trials).[31-33,44,74,92,98]

Table 88. Evidence summary table: haloperidol versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Incidence of patients with AEs[31,73,98]	3	1713	1.11 (1.06, 1.17)	0%	aripiprazole
Withdrawals due to AEs[31-33,44,76,92,98]	7	3035	1.25 (1.06, 1.47)	0%	aripiprazole

AE = adverse events; CI = confidence intervals; I^2 = I–squared

Table 89. Evidence summary table: haloperidol versus aripiprazole – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Mania[33]	1	332	0.20 (0.05, 0.91)	NE	haloperidol
CNS					
Dizziness[31,44,92]	3	963	0.53 (0.31, 0.90)	0%	haloperidol
Somnolence[31,33,44,74,92,98]	6	2893	1.39 (1.03, 1.87)	0%	aripiprazole
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia[32,33]	2	679	3.67 (2.16, 6.24)	70%	aripiprazole
EPS					
Akathisia[31-33,74,76,92,98]	7	2979	2.04 (1.70, 2.44)	0%	aripiprazole
Dystonia[31]	1	295	7.83 (1.47, 41.76)	NE	aripiprazole
EPS[32,33,44,74,92,98]	6	2945	2.22 (1.37, 3.59)	83%	aripiprazole
Rigidity[33]	1	332	8.10 (1.89, 34.66)	NE	aripiprazole
Tremor[32,33,76,92,98]	5	2380	1.99 (1.42, 2.78)	4%	aripiprazole
GI					
Dyspepsia[74]	1	304	9.12 (1.17, 71.10)	NE	aripiprazole
Nausea or vomiting[31,44,74,92]	4	1267	0.49 (0.28, 0.85)	0%	haloperidol
Ophthalmology					
Blurred vision[92]	1	308	5.23 (1.42, 19.30)	NE	aripiprazole

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I^2 = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Asenapine

A single trial[67] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving asenapine. Oral hypoesthesia and somnolence were less frequent with haloperidol. Hyperprolactinemia, dystonia, and EPS were less frequent with asenapine (Table 90). There were no differences in the other reported AEs (Appendix N, Tables 131 and 132).

Table 90. Evidence summary table: haloperidol versus asenapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
CNS					
Oral hypoesthesia[97]	1	335	0.04 (0.00, 0.69)	NE	haloperidol
Somnolence[97]	1	335	0.21 (0.05, 0.90)	NE	haloperidol
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia[97]	1	335	2.30 (1.02, 5.15)	NE	asenapine
EPS					
Dystonia[97]	1	335	3.51 (1.33, 9.24)	NE	asenapine
EPS[97]	1	335	2.07 (1.40, 3.07)	NE	asenapine

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; I^2 = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Clozapine

Six trials[55,95,105,126,145,155] and two cohort studies[162,163] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving clozapine (Table 91). The statistically significant findings are presented in Table 92. Other reported AEs did not differ between groups (Appendix N, Tables 133 and 134).

General Measures

A single cohort study found less incidence of mortality with clozapine.[163] The incidence of patients with AEs (1 trial)[126] and withdrawals due to AEs (5 trials),[55,95,105,126,145] was not different between groups.

Specific Measures

Behavior and Psychosis

Single trials reported less frequent incidence of irritability[155] and overt aggression[145] with clozapine. One trial found no difference between groups in clinical deterioration conducive to termination.[145]

BMI and Weight

No difference between groups was reported for weight gain (2 trials).[105,145]

Cardiovascular

Single trials found no differences in incidence of hypertension,[55] hypertensive episodes,[145] intrathoracic oppression,[155] orthostatic hypotension,[155] and palpitation.[155]

Cholinergic and Anticholinergic

Dry mouth (2 trials)[55,155] was less frequent with clozapine. Hypersalivation (1 trial)[55] was less frequent with haloperidol.

CNS

No differences between groups were found for the incidence of CNS abnormalities, including dizziness (2 trials),[55,155] drowsiness (1 trial),[155] dysarthria (1 trial),[155] sedation (1 trial),[55] seizures (1 trial),[145] and seizures conducive to termination (1 trial).[145]

Dermatology

Single trials reported no difference in the incidence of pruritus[155] and rash.[155]

Endocrine (Prolactin and Thyroid)

A single trial[155] reported no difference in the incidence of abnormal menstruation.

EPS

A single trial[155] found less frequent incidence of hyperkinesia with clozapine and no difference between groups in the incidence of hypertonia. One cohort study[162] reported less frequent incidence of tardive dyskinesia with clozapine.

Gastrointestinal

The incidence of nausea or vomiting (2 trials)[55,155] was less frequent with haloperidol. There was no difference in the incidence of constipation (2 trials),[55,155] diarrhea (2 trials),[55,155] loss of appetite (1 trial),[155] and other gastrointestinal abnormalities (1 trial).[155]

Genital, Urinary, and Breast

A single trial[55] reported no difference in the incidence of enuresis.

Hematology

There were no differences between groups in the incidence of agranulocytosis (2 trials),[126,145] bruising (1 trial),[55] hematological problems conducive to termination (1 trial),[145] leukopenia (1 trial),[126] and neutropenia (2 trials).[126,145]

Metabolic

A single trial[105] reported less frequent incidence of abnormal glucose levels and emergent metabolic syndrome with haloperidol. The trial found no difference in hypercholesterolemia and hypertriglyceridemia.

Ophthalmology

A single trial[155] reported no difference in ophthalmic disturbances.

Respiratory and Airway

Two trials[55,155] reported no difference in upper respiratory disturbances.

Sleep

A single trial[155] reported less frequent incidence of insomnia with clozapine.

Systemic AEs

The incidence of the following AEs was not different between groups: headache (1 trial),[155] fever (2 trials),[55,155] intercurrent illnesses conducive to termination (1 trial),[145] malaise (1 trial),[55] sweating (1 trial),[155] and weakness (1 trial).[155]

Table 91. Evidence summary table: haloperidol versus clozapine – general AEs (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Mortality (Cohort)[163]	1	49625	1.98 (1.30, 3.00)	NE	clozapine

AE = adverse events; I^2 = I–squared; KQ = Key Question; NE = not estimable

Table 92. Evidence summary table: haloperidol versus clozapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Irritability[155]	1	88	3.21 (1.26, 8.15)	NE	clozapine
Overt aggression[145]	1	77	1.66 (1.03, 2.66)	NE	clozapine
Cholinergic and Anticholinergic					
Dry mouth[55,155]	2	163	2.81 (1.61, 4.92)	0%	clozapine
Hypersalivation[55]	1	75	0.23 (0.12, 0.46)	NE	haloperidol
EPS					
Hyperkinesia[155]	1	88	2.01 (1.13, 3.56)	NE	clozapine
Tardive Dyskinesia (Cohort)[162]	1	333	34.50 (2.07, 573.55)	NE	clozapine
GI					
Nausea or vomiting[55,155]	2	163	0.44 (0.21, 0.93)	17%	haloperidol
Metabolic					
Abnormal Glucose levels[105]	1	73	0.05 (0.00, 0.80)	NE	haloperidol
Metabolic syndrome (emergent)[105]	1	73	0.27 (0.10, 0.75)	NE	haloperidol
Sleep					
Insomnia[155]	1	88	3.44 (1.51, 7.84)	NE	clozapine

AE = adverse event; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I^2 = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Olanzapine

Twenty-seven trials[43,49-51,54,56,71,73,78,84,88,91,101,104-106,108,110,124,127,129,140-142,145,147,159] and two cohort studies[162,163] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving olanzapine (Table 93). The statistically significant findings are presented in Table 94. Other reported AEs did not differ between groups (Appendix N, Tables 135 and 136).

General Measures

The incidence of withdrawals due to AEs (21 trials)[43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159] was reported less frequently with olanzapine. There was some suggestion of publication bias based on Egger's test ($p = 0.02$) and some funnel plot asymmetry (Appendix K, Funnel plot 13). No difference was found for patients with AEs (1 trial),[73] persistence and reversibility of AE (1 trial),[88] and SAEs (3 trials).[91,104,147]

Specific Measures

Behavior and Psychosis

In single trials, the incidence of anorexia,[88] decreased appetite,[141] and conversion symptoms[141] were less frequent with olanzapine, whereas the incidence of excessive appetite (1 trial)[141] was less frequent with haloperidol. Other behavioral and psychotic-related AEs were not different between groups: abnormal thinking (1 trial),[101] accommodation disturbance (1 trial),[159] agitation (2 trials),[49,101] anxiety (4 trials),[49,88,101,147] behavioral deterioration (2 trials),[73,84] depression (1 trial),[101] excitement (1 trial),[88] hallucinations (2 trials),[84,101] nervousness (2 trials),[49,101] overt aggression or violent behavior (3 trials),[49,110,145] paranoia (1 trial),[101] personality disorder (1 trial),[49] suicidal ideation (1 trial),[110] and suicide (1 trial),[88] suicide attempt (1 trial).[88]

BMI and Weight

The incidence of patients categorized as overweight or obese (2 trials)[91,129] and weight gain (15 trials)[49,71,88,91,101,104,105,108,127,129,140-142,145,159] was less frequent with haloperidol. There was no difference between groups in patients with weight loss (2 trials).[88,141]

Cardiovascular

A single trial found fewer palpitations with olanzapine.[141] No difference between groups was found for ECG abnormalities (2 trials),[56,91] hypertensive episodes (1 trial),[145] and hypotension (1 trial).[56]

Cholinergic and Anticholinergic

AEs. The incidence of dry mouth (5 trials)[49,71,101,141,159] was less frequent with haloperidol. The incidence of hypersalivation (6 trials)[50,71,88,140,141,159] was less frequent with olanzapine.

CNS

The incidence of drowsiness (1 trial),[141] gait abnormalities (1 trial),[88] heaviness in the extremities (1 trial),[141] hypokinesia (4 trials),[71,140,141,159] and hypotonia (1 trial)[141] was less frequent with olanzapine. There were no differences between groups for asthenia (3 trials),[49,71,159] concentration difficulty (1 trial),[71] dizziness (3 trials),[49,101,140] seizures (1 trial),[145] and somnolence (6 trials).[49,71,88,101,140,159]

Dermatology

A single trial[147] reported no difference in the incidence of maculopapular rash.

Endocrine (Prolactin and Thyroid)

In a single trial,[141] the incidence of hot flashes was less frequent with olanzapine. There was no difference in the incidence of amenorrhea (1 trial).[71] The pooled results for hyperprolactinemia (3 trials)[50,91,108] were not reported because there was marked heterogeneity between the trials (I^2 = 97 percent).

EPS

The incidence of the following EPS-related AEs were less frequent with olanzapine: akathisia (14 trials),[49-51,56,71,88,91,101,104,108,127,140,141,159] ataxia (1 trial),[141] bradykinesia (1 trial),[88] dyskinesia (4 trials),[50,91,140,141] dystonia (8 trials),[49,50,56,91,104,140,147,159] EPS (6 trials),[50,104,106,140,141,147] hypertonia (4 trials),[49,50,140,141] parkinsonism (8 trials),[51,56,71,84,88,91,108,147] rigidity (2 trials),[71,159] and tremor (9 trials).[49,50,71,88,101,104,140,141,159] Single trials found no difference in the incidence of neuroleptic malignant syndrome[147] and tardive dyskinesia.[140]

Gastrointestinal

The incidence of nausea or vomiting (5 trials)[49,88,101,141,141] was less frequent with olanzapine. There was no difference in the incidence of constipation (3 trials),[49,101,159] diarrhea (1 trial),[101] and dyspepsia (1 trial).[49]

Genital, Urinary, and Breast

In single trials, difficult micturition[141] was less frequent with olanzapine. No differences were found between groups for ejaculatory dysfunction,[71] erectile dysfunction,[71] and micturition disturbances.[159]

Hematology

The incidence of the following hematological disorders were not different between groups: agranulocytosis (2 trials),[141,145] eosinophilia (1 trial),[50] hematological problems conducive to termination (1 trial),[145] and neutropenia (1 trial).[145]

Hepatobiliary

The incidence of abnormalities of serum glutamic oxaloacetic transaminase (1 trial)[108] and serum glutamic pyruvic transaminase (2 trials)[49,108] were less frequent with haloperidol. In single trials, there was no difference in the incidence of elevated alanine aminotransferase[50] or increased gamma-glutamyl transpeptidase.[50]

Metabolic

The incidence of the following metabolic disorders was less frequent with haloperidol: hypercholesterolemia (2 trials),[91,105] hyperglycemia (2 trials),[91,105] hypertriglyceridemia (2 trials),[91,105] and low levels of high-density lipoprotein (1 trial).[91] There were no differences between groups in the incidence of diabetes (1 trial)[129] or metabolic syndrome (2 trials).[105,129]

Ophthalmology

A single trial[141] reported less blurred vision with olanzapine.

Respiratory and Airway

The incidence of rhinitis was not different between groups (2 trials).[49,101]

Sleep

The incidence of sleep disturbances, including early awakening (1 trial),[141] increased dreams or nightmares (1 trial),[141] and insomnia (7 trials),[49,50,88,101,104,127,141] were less frequent with olanzapine.

Systemic AEs

In single trials, chills[141] and increased perspiration[141] were less frequent with olanzapine. In contrast, fever[140] and infection[140] were less frequent with haloperidol. No differences were found between groups for the following other systemic AEs: headache (3 trials),[49,50,101] injury (1 trial),[49] intercurrent illnesses conducive to termination (1 trial),[145] malaise (1 trial),[88] pain (2 trials),[49,101] and tension (1 trial).[159]

Table 93. Evidence summary table: haloperidol versus olanzapine – general measures with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Withdrawals due to adverse events[43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159]	21	5351	1.87 (1.55, 2.27)	0%	olanzapine

I^2 = I-squared; KQ = Key Question

Table 94. Evidence summary table: haloperidol versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Anorexia[88]	1	182	3.66 (1.25, 10.69)	NE	olanzapine
Appetite (decreased)[141]	1	1996	1.56 (1.25, 1.96)	NE	olanzapine
Appetite (excessive)[141]	1	1996	0.51 (0.41, 0.64)	NE	haloperidol
Conversion symptoms[141]	1	1996	2.34 (1.12, 4.88)	NE	olanzapine
BMI and Weight					
Overweight or obese[91,129]	2	274	0.35 (0.21, 0.58)	0%	haloperidol
Weight gain[49,71,88,91,101,104,105,108,127,129,140-142,145,159]	15	4600	0.47 (0.37, 0.61)	75%	haloperidol
Cardiovascular					
Palpitations[141]	1	1996	1.48 (1.09, 2.02)	NE	olanzapine
Cholinergic and Anticholinergic					
Dry mouth[49,71,101,141,159]	5	2657	0.75 (0.62, 0.91)	0%	haloperidol
Hypersalivation[50,71,88,140,141,159]	6	3200	3.38 (1.79, 6.38)	49%	olanzapine
CNS					
Drowsiness[141]	1	1996	1.19 (1.02, 1.38)	NE	olanzapine
Gait abnormalities[88]	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Heaviness in extremities[141]	1	1996	1.40 (1.11, 1.77)	NE	olanzapine
Hypokinesia[71,140,141,159]	4	2587	3.01 (1.88, 4.82)	7%	olanzapine
Hypotonia[141]	1	1996	1.68 (1.03, 2.72)	NE	olanzapine
Endocrine (Prolactin and Thyroid)					
Hot flashes[141]	1	1996	1.62 (1.06, 2.49)	NE	olanzapine

Table 94. Evidence summary table: haloperidol versus olanzapine – specific AEs with significant differences (KQ3) (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
EPS					
Akathisia[49-51,56,71,88,91,101,104,108,127,140,141,159]	14	5031	3.11 (2.43, 3.98)	38%	olanzapine
Ataxia[141]	1	1996	1.84 (1.01, 3.35)	NE	olanzapine
Bradykinesia[88]	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Dyskinesia[50,91,140,141]	4	3088	3.55 (2.01, 6.27)	10%	olanzapine
Dystonia[49,50,56,91,104,140,147,159]	8	2144	5.01 (2.70, 9.28)	0%	olanzapine
EPS[50,104,106,140,141,147]	6	3445	3.88 (2.19, 6.85)	69%	olanzapine
Hypertonia[49,50,140,141]	4	3147	2.54 (1.65, 3.91)	55%	olanzapine
Parkinsonism[51,56,71,84,88,91,108,147]	8	1283	4.28 (2.49, 7.35)	50%	olanzapine
Rigidity[71,159]	2	138	10.65 (2.08, 54.50)	0%	olanzapine
Tremor[49,50,71,88,101,104,140,141,159]	9	3999	2.30 (1.59, 3.34)	58%	olanzapine
Genital, Urinary, and Breast					
Difficult micturition[141]	1	1996	1.68 (1.11, 2.54)	NE	olanzapine
GI					
Nausea or vomiting[49,88,101,141,141]	5	4697	1.43 (1.06, 1.92)	34%	olanzapine
Hepatobiliary					
SGOT abnormality[108]	1	263	0.41 (0.28, 0.58)	NE	haloperidol
SGPT abnormality[49,108]	2	530	0.46 (0.35, 0.62)	0%	haloperidol
Metabolic					
Hypercholesterolemia[91,105]	2	281	0.43 (0.26, 0.72)	0%	haloperidol
Hyperglycemia[91,105]	2	281	0.28 (0.12, 0.66)	0%	haloperidol
Hypertriglyceridemia[91,105]	2	281	0.53 (0.30, 0.92)	0%	haloperidol
HDL (low)[91]	1	208	0.38 (0.16, 0.94)	NE	haloperidol
Ophthalmology					
Blurred vision[141]	1	1996	1.40 (1.10, 1.78)	NE	olanzapine
Sleep					
Early awakening[141]	1	1996	1.49 (1.24, 1.79)	NE	olanzapine
Increased dreams/nightmares[141]	1	1996	1.31 (1.05, 1.63)	NE	olanzapine
Insomnia[49,50,88,101,104,127,141]	7	3717	1.36 (1.03, 1.80)	49%	olanzapine
Systemic AE					
Chills[141]	1	1996	1.74 (1.19, 2.52)	NE	olanzapine
Fever[140]	1	453	0.05 (0.00, 0.86)	NE	haloperidol
Infection[140]	1	453	0.27 (0.08, 0.93)	NE	haloperidol
Increased perspiration[141]	1	1996	1.91 (1.44, 2.54)	NE	olanzapine

AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; HDL = high-density lipoprotein; I^2 = I-squared; KQ = Key Question; NE = not estimable; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Haloperidol Versus Quetiapine

Ten trials[46,47,65,68,73,79,80,91,115,123] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving quetiapine. The statistically significant findings are presented in Table 95. Other reported AEs did not differ between groups (Appendix N, Tables 137 and 138).

General Measures

The incidences of patients with AEs (3 trials),[68,73,79] SAEs (1 trial),[91] and withdrawals due to AEs (8 trials)[46,47,68,79,80,91,115,123] were not different between groups.

Specific Measures

Behavior and Psychosis

A single trial[68] reported less frequent asthenia with haloperidol. The following other AEs related to behavior and psychosis were not different between groups: agitation (4 trials),[46,68,115,123] anxiety (1 trial),[68] depression (1 trial),[115] deterioration (1 trial),[73] fatigue (1 trial),[123] and irritability (1 trial).[123]

BMI and Weight

Weight gain (3 trials)[46,91,123] was less frequent with haloperidol. A single trial[91] reported no difference between groups in the incidence of overweight patients.

Cardiovascular

Orthostatic hypotension (3 trials),[46,68,115] was less frequent with haloperidol. The incidence of ECG abnormalities (2 trials)[46,91] was not different between groups.

Cholinergic and Anticholinergic

Dry mouth (3 trials)[68,115,123] was less frequent with haloperidol; hypersalivation (2 trials)[68,123] did not differ between groups.

CNS

Somnolence (4 trials)[46,68,115,123] was less frequent with haloperidol. The incidence of other CNS abnormalities, including dizziness (2 trials),[46,68] drowsiness (1 trial),[123] sedation (1 trial)[123] did not differ between groups.

Dermatology

A single trial[123] reported no difference in the incidence of dry skin or rash.

Endocrine (Prolactin and Thyroid)

Hyperprolactinemia (3 trials)[68,79,91] was less frequent with quetiapine. A single trial found less frequent thyroid function test abnormalities with haloperidol.[68] Single trials reported no difference for the following endocrine abnormalities: amenorrhea or menstrual cycle irregularities,[123] cold flashes,[123] and galactorrhea.[47]

EPS

Akathisia (5 trials),[46,68,79,91,115] parkinsonism (2 trials),[46,91] and tremors (2 trials)[68,115] were less frequent with quetiapine. The following EPS-related AEs showed no difference between groups: akinesia (1 trial),[68] cogwheel rigidity (1 trial),[68] dyskinesia (1 trial),[91] dystonia (3 trials),[46,68,91] fine tremors (1 trial),[123] hypertonia (2 trials),[68,79] involuntary movement of the jaw (1 trial),[123] neck rigidity (1 trial),[68] oculogyric crisis (1 trial),[68] stiffness (1 trial),[123] tardive dyskinesia (1 trial),[65] and twitching of the extremities (1 trial).[123] Pooled results for EPS (5 trials)[46,68,79,80,115] were not reported because of marked heterogeneity between the trials ($I^2 = 90$ percent).

Gastrointestinal

Constipation (2 trials)[46,68] was less frequent with haloperidol. A single trial[46] reported no difference in the rate of dyspepsia.

Hematology

Single trials found no differences in the incidence of agranulocytosis[46] or leucopenia.[68]

Hepatobiliary

A single trial[68] reported no difference between groups in elevated liver transaminases.

Metabolic

Single trials reported no differences between groups in the incidence of low levels of high-density lipoprotein,[91] hypercholesterolemia,[91] hyperglycemia,[91] and hypertriglyceridemia.[91]

Ophthalmology

A single trial[123] reported no difference in the incidence of blurred vision.

Sleep

The incidence of insomnia (4 trials)[46,68,115,123] did not differ between groups.

Systemic AEs

The incidence of headaches (4 trials)[46,68,115,123] did not differ between groups.

Table 95. Evidence summary table: haloperidol versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Asthenia[68]	1	448	0.29 (0.12, 0.71)	NE	haloperidol
BMI and Weight					
Weight gain[46,91,123]	3	542	0.59 (0.39, 0.89)	0%	haloperidol
Cardiovascular					
Orthostatic hypotension[46,68,115]	3	959	0.49 (0.25, 0.94)	0%	haloperidol
Cholinergic and Anticholinergic					
Dry mouth[68,115,123]	3	674	0.32 (0.15, 0.65)	0%	haloperidol
CNS					
Somnolence[46,68,115,123]	4	984	0.57 (0.39, 0.84)	0%	haloperidol
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia[68,79,91]	3	943	2.24 (1.04, 4.80)	89%	quetiapine
Thyroid function test abnormalities[68]	1	448	0.05 (0.00, 0.79)	NE	haloperidol

Table 95. Evidence summary table: haloperidol versus quetiapine – specific AEs with significant differences (KQ3) (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
EPS					
Akathisia[46,68,79,91,115]	5	1454	3.51 (1.84, 6.72)	68%	quetiapine
Parkinsonism[46,91]	2	517	4.04 (1.97, 8.26)	53%	quetiapine
Tremor[68,115]	2	649	3.80 (2.12, 6.81)	0%	quetiapine
GI					
Constipation[46,68]	2	758	0.45 (0.22, 0.93)	0%	haloperidol

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I^2 = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Risperidone

Twenty-eight trials[52,53,59-61,64,71-73,81,82,85,90,101,117,118,120,124,128,132,136,138,139,145,146,149-151] and one cohort study[163] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving risperidone (Table 96). The statistically significant findings are presented in Table 97. Other reported AEs did not differ between groups (Appendix N, Tables 139 and 140).

General Measures

The incidences of patients with AEs (8 trials),[72,73,81,85,117,128,136,151] mortality (1 cohort study),[163] and withdrawals due to AEs (23 trials),[52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151] were less frequent with risperidone. There was no indication of publication bias for withdrawals due to AEs based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 14). Single trials showed no difference for the incidence of AEs resolved spontaneously by 24 hours[151] and SAEs.[52]

Specific Measures

Behavior and Psychosis

Asthenia (5 trials),[52,71,117,120,149] was less frequent with risperidone. No differences between groups were found for the following AEs: abnormal thinking (1 trial),[101] accommodation disturbances (2 trials),[120,149] agitation (4 trials),[61,72,81,101] anxiety (3 trials),[61,81,101] concentration difficulty (4 trials),[64,71,117,120] decreased appetite (1 trial),[64] depression (2 trials),[101,118] deterioration (1 trial),[73] drug overdose (1 trial),[118] decreased sexual desire (2 trials),[120,149] fatigue (2 trials),[60,64] hallucination (1 trial),[101] increased appetite (1 trial),[64] manic reaction (1 trial),[128] nervousness (1 trial),[101] paranoia (1 trial),[101] and sexual disturbances (1 trial).[52]

BMI and Weight

A single trial[101] reported less incidence of weight gain with haloperidol.

Cardiovascular

The groups did not differ in the incidence of the following cardiovascular abnormalities: ECG abnormalities (1 trial),[128] hypotension (1 trial),[61] orthostatic tachycardia (1 trial),[61] orthostatic hypotension (3 trials),[52,61,64] and palpitations (2 trials).[52,64]

Cholinergic and Anticholinergic

The incidence of decreased salivation (1 trial),[71] dry mouth (4 trials),[52,60,64,101] and hypersalivation (1 trial)[85] did not differ between groups.

CNS

No differences were found between groups for dizziness (3 trials),[101,128,151] sedation (1 trial),[64] somnolence (5 trials),[52,53,101,128,151] and vertigo (2 trials).[52,64]

Endocrine (Prolactin and Thyroid)

The incidence of amenorrhea (4 trials)[64,71,120,149] and galactorrhea (1 trial)[132] did not differ between groups.

EPS

Akathisia (7 trials),[52,60,71,101,139,146,149] EPS (5 trials),[61,117,128,138,151] and tremor (4 trials)[52,85,101,128] were less frequent with risperidone. There was no difference between groups for dystonia (3 trials)[60,139,149] or oculogyric crisis (1 trial).[85]

Gastrointestinal

The incidence of constipation (7 trials),[52,53,64,101,120,128,149] diarrhea (1 trial),[101] dyspepsia (1 trial),[128] nausea or vomiting (5 trials)[53,61,64,85,101] did not differ between groups.

Genital, Urinary, and Breast

The incidence of breast tension (1 trial),[64] dry vagina (1 trial),[149] ejaculatory dysfunction (4 trials),[64,71,120,149] erectile dysfunction (3 trials),[64,71,120] gynecomastia (1 trial),[132] and micturition disturbances (1 trial)[52] did not differ between groups.

Hematology

A single trial[145] reported no difference in the incidence of agranulocytosis.

Ophthalmology

Two trials[60,64] reported no difference in the incidence of blurred vision.

Respiratory and Airway

A single trial[101] reported no difference in the incidence of rhinitis.

Sleep

The incidence of insomnia (6 trials)[52,61,81,101,120,151] and sleep disorders (2 trials)[52,85] did not differ between groups.

Systemic AEs

No differences were found between groups in the incidence headaches (9 trials),[52,53,61,64,81,85,101,128,151] increased sweating (2 trials),[52,64] infection (1 trial),[53] and pain (1 trial).[101]

Table 96. Evidence summary table: haloperidol versus risperidone – general measures of AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Incidence of patients with adverse events[72,73,81,85,117,128,136,151]	8	1313	1.20 (1.01, 1.42)	84%	risperidone
Mortality (Cohort)[163]	1	63352	1.70 (1.31, 2.20)	NE	risperidone
Withdrawals due to adverse events[52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151]	23	4421	1.27 (1.04, 1.55)	0%	risperidone

AE = adverse events; I^2 = I-squared; KQ = Key Question; NE = not estimable

Table 97. Evidence summary table: haloperidol versus risperidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Asthenia[52,71,117,120,149]	5	1596	1.20 (1.02, 1.41)	0%	risperidone
BMI and Weight					
Weight gain[101]	1	255	0.19 (0.05, 0.81)	NE	haloperidol
EPS					
Akathisia[52,60,71,101,139,146,149]	7	619	1.79 (1.31, 2.44)	0%	risperidone
EPS[61,117,128,138,151]	5	675	1.86 (1.46, 2.36)	0%	risperidone
Tremor[52,85,101,128]	4	478	2.09 (1.23, 3.53)	0%	risperidone

AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms or syndrome; I^2 = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Ziprasidone

Nine trials [57,69,73,83,86,91,116,122,144] reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving ziprasidone (Table 98). The statistically significant findings are presented in Table 99. Other reported AEs did not differ between groups (Appendix N, Tables 141, 142, and 143).

General Measures

The incidences of patients with AEs (6 trials)[57,69,73,83,86,144] and withdrawals due to AEs (6 trials)[57,83,86,91,116,144] were less frequent with ziprasidone. No difference between groups was found for mortality (2 trials)[116,144] and SAEs (4 trials).[57,86,91,144]

Specific Measures

Behavior and Psychosis

The incidence of agitation (2 trials),[86,116] anxiety (3 trials),[86,116,144] asthenia (2 trials),[86,116] depression (2 trials),[86,144] clinical deterioration (1 trial),[73] and hallucinations (1 trial)[86] did not differ between groups.

BMI and Weight

The incidence of overweight patients (1 trial)[91] and patients with weight gain (2 trials)[91,144] or weight loss (1 trial)[144] did not differ between groups.

Cardiovascular

The incidence of cardiovascular AEs (1 trial),[116] ECG abnormalities (6 trials),[57,86,91,116,122,144] hypertension (1 trial),[116] hypotension (1 trial),[116] and syncope (1 trial)[116] did not differ between groups.

Cholinergic and Anticholinergic

Two studies found no difference in the incidence of dry mouth.[86,116]

CNS

A single trial[144] found that hypokinesia and hypotonia were less frequent with ziprasidone. The incidence of dizziness (3 trials)[86,116,144] and somnolence (5 trials),[57,86,116,122,144] did not differ between groups.

Dermatology

A single trial[116] reported no difference in the incidence of injection-site pain.

Endocrine (Prolactin and Thyroid)

Two trials[57,91] reported no difference in the incidence of hyperprolactinemia.

EPS

Dystonia (3 trials),[57,91,144] EPS (5 trials),[57,69,116,122,144] hypertonia (3 trials),[57,86,116] movement disorder (1 trial),[86] and tremor (5 trials)[57,86,116,122,144] were less frequent with ziprasidone. No differences between groups were found in the incidence of akathisia (6 trials),[57,86,91,116,122,144] dyskinesia (1 trial),[91] parkinsonism (1 trial),[91] psychosis (1 trial),[86] and tardive dyskinesia (1 trial).[86]

Gastrointestinal

The incidence of dyspepsia (1 trial)[144] and nausea or vomiting (2 trials)[86,116] did not differ between groups.

Metabolic

A single study found no difference between groups in the incidence of low levels of high-density lipoprotein, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia.[91]

Ophthalmology

A single trial[116] reported no difference in the incidence of abnormal vision.

Sleep

The incidence of insomnia (4 trials)[57,86,116,122] did not differ between groups.

Systemic AEs

The incidence of headaches (3 trials),[86,116,144] malaise (1 trial),[116] and sweating (1 trial)[116] did not differ between groups.

Table 98. Evidence summary table: haloperidol versus ziprasidone – general measures with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Incidence of patients with adverse events[57,69,73,83,86,144]	6	1448	1.13 (1.03, 1.23)	31%	ziprasidone
Withdrawals due to adverse events[57,83,86,91,116,144]	6	1551	1.73 (1.30, 2.32)	0%	ziprasidone

I^2 = I-squared; KQ = Key Question

Table 99. Evidence summary table: haloperidol versus ziprasidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
CNS					
Hypokinesia[144]	1	350	6.21 (1.41, 27.34)	NE	ziprasidone
Hypotonia[144]	1	350	5.86 (1.75, 19.65)	NE	ziprasidone
EPS					
Dystonia[57,91,144]	3	1102	2.19 (1.34, 3.60)	15%	ziprasidone
EPS[57,69,116,122,144]	5	1594	2.34 (1.56, 3.53)	63%	ziprasidone
Hypertonia[57,86,116]	3	926	2.45 (1.52, 3.94)	0%	ziprasidone
Movement disorder[86]	1	301	2.73 (1.77, 4.19)	NE	ziprasidone
Tremor[57,86,116,122,144]	5	1875	2.55 (1.79, 3.63)	4%	ziprasidone

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I^2 = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Aripiprazole

A single trial[93] reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving aripiprazole (Table 100). The incidence of dizziness, ECG abnormalities, hyperprolactinemia, and injury was less frequent with aripiprazole. Other reported AEs were not different between groups (Appendix N, Tables 144 and 145).

Table 100. Evidence summary table: perphenazine versus aripiprazole – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Behavior and Psychosis					
Dizziness[93]	1	300	5.27 (1.18, 23.66)	NE	aripiprazole
Cardiovascular					
ECG abnormalities[93]	1	300	15.82 (2.12, 118.27)	NE	aripiprazole
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia[93]	1	300	13.89 (6.25, 30.86)	NE	aripiprazole
Systemic AE					
Injury[93]	1	300	4.75 (1.04, 21.60)	NE	aripiprazole

AE = adverse event; ECG = electrocardiogram; I^2 = I–squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Olanzapine

A single trial[23] reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving olanzapine (Table 101). Weight gain was less frequent with perphenazine. The incidence of patients with Abnormal Involuntary Movement Scale (AIMS) global severity score $\geq$2 and insomnia was less frequent with olanzapine. Other reported AEs were not different between groups (Appendix N, Tables 146 and 147).

Table 101. Evidence summary table: perphenazine versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
BMI and Weight					
Weight gain[23]	1	597	0.41 (0.28, 0.60)	NE	perphenazine
EPS					
AIMS global severity score ≥2[23]	1	597	1.65 (1.07, 2.54)	NE	olanzapine
Sleep					
Insomnia[23]	1	597	1.54 (1.12, 2.13)	NE	olanzapine

AE = adverse events; AIMS = Abnormal Involuntary Movement Scale; BMI = body mass index; EPS = extrapyramidal symptoms or syndrome; I^2 = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Quetiapine

A single trial[23] reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving quetiapine (Table 102). Anticholinergic AEs was less frequent with perphenazine. The incidence of patients with AIMS global severity score ≥2 was less frequent with quetiapine. Other reported AEs were not different between groups (Appendix N, Tables 148 and 149).

Table 102. Evidence summary table: perphenazine versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Cholinergic and Anticholinergic					
Anticholinergic side effects[23]	1	598	0.70 (0.53, 0.93)	NE	perphenazine
EPS					
AIMS global severity score ≥2[23]	1	598	1.76 (1.13, 2.75)	NE	quetiapine

AE = adverse events; AIMS = Abnormal Involuntary Movement Scale; EPS = extrapyramidal symptoms or syndrome; I^2 = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Risperidone

A single trial[23] reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving risperidone (Table 103). Incontinence or nocturia was less frequent with perphenazine. Other reported AEs were not different between groups (Appendix N, Tables 150 and 151).

Table 103. Evidence summary table: perphenazine versus risperidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Genital, Urinary, and Breast					
Incontinence or nocturia[23]	1	602	0.31 (0.13, 0.75)	NE	perphenazine

AE = adverse events; I^2 = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Ziprasidone

A single trial[23] found no differences between perphenazine and ziprasidone in the incidence of any AEs (Appendix N, Tables 152 and 153).

Thioridazine Versus Clozapine

A single cohort study[163] found lower incidence of mortality with clozapine compared with thiordazine (Table 104; Appendix N, Table 154).

Table 104. Evidence summary table: thioridazine versus clozapine – general AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Mortality (Cohort)[163]	1	32280	2.12 (1.38, 3.26)	NE	clozapine

AE = adverse events I^2 = I-squared; KQ = Key Question; NE = not estimable

Thioridazine Versus Risperidone

A single cohort study[163] found lower incidence of mortality with risperidone compared with thiordazine (Table 105; Appendix N, Table 155).

Table 105. Evidence summary table: thioridazine versus risperidone – general AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I^2	Less With
Mortality (Cohort)[163]	1	46007	1.82 (1.37, 2.40)	NE	risperidone

AE = adverse event; I^2 = I-squared; KQ = Key Question; NE = not estimable

Summary and Discussion

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness and safety of first- (FGAs) versus second-generation antipsychotics (SGAs) in adults with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. We included studies that directly compared one FGA versus one SGA. We did not include: studies comparing various FGAs or those comparing various SGAs; trials with no active comparator (e.g., no treatment or placebo-controlled trials); or those trials comparing antipsychotics not approved by the U.S. Food and Drug Administration (FDA) or no longer available in the U.S. (Appendix O). The strength of evidence (SoE) for core illness symptoms and key adverse events (AEs) is summarized by comparison in the tables below.

We identified a large number of studies comparing individual FGAs with individual SGAs, with the majority of studies being efficacy trials.[41] The decision to limit the scope of the review to only randomized controlled trials (RCTs) and non-RCTs with additional input from long-term cohort studies was based on a previous literature search and expert opinion. The technical expert panel felt that there were sufficient RCTs in this area to adequately address the questions. To supplement the RCTs (which are often short-term), it was decided that long-term cohort studies would also be included as these could provide data on long-term outcomes (e.g. mortality, tardive dyskinesia, diabetes mellitus and metabolic syndrome), that are not usually available in the more rigorously designed RCTs. Overall, 113 studies provided data on 22 different comparisons for patients with schizophrenia or schizophrenia-related psychoses. Fewer studies provided evidence comparing antipsychotic drugs in patients with bipolar disorder (n = 11). One trial included patients with schizophrenia or bipolar disorder. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Although many studies reported data for core illness symptoms, a total of 111 scales and subscales or composite outcomes were used across studies. The heterogeneity in outcome assessment tools and the small number of studies within specific comparisons precluded drawing firm conclusions that may be directly relevant to front-line clinical decisions. Further, the primary outcomes were most often for core illness symptoms and did not cover the full spectrum of outcomes that clinicians and patients need information about for medication decisionmaking (e.g., patient employment and functioning). Outcomes potentially important to patients were rarely assessed in the studies, including health-related quality of life, social and occupational functioning, legal interactions, and certain symptoms, such as depression or anxiety. This limits the potential applicability to real-life functions and naturalistic outcomes. For future reviews, these important outcomes may be searched for in long-term observational studies, but it is unclear whether these types of outcomes are assessed in the research literature.

Data were provided primarily from randomized controlled trials (RCTs); however, in our quality assessment, most of the trials were found to have unclear risk of bias due to insufficient reporting of the methods to prevent selection bias (i.e., random sequence generation and allocation concealment) and performance bias (i.e., proper blinding of participants and study personnel). Inadequate randomization and allocation concealment have been associated with exaggerated estimates of treatment effects for a number of medications in different fields of on average 12 and 18 percent, respectively.[164,165] Within this clinical field, trials that are single-blind or open-label have been found to favor the SGAs over FGAs;[6] hence, results need to be interpreted in light of these limitations of the primary studies.

Despite our efforts to identify long-term safety data from observational studies, only two retrospective cohort studies provided data for a minimum 2-year followup period. In contrast, we included eight RCTs providing data over a followup period of 2 or more years. Short-term efficacy trials, which are accepted by the regulatory authorities, may not identify time-dependent AEs, such as tardive dyskinesia, diabetes mellitus, metabolic syndrome or mortality. The optimal and minimal acceptable duration of followup in trials remains to be determined, but may arbitrarily be set at 2 years duration in order to capture important clinical and patient-related outcomes (e.g., occupational functioning measures and long-term safety). Even with long-term trials, it is important that researchers document and report these outcomes as it is so far evidenced that there is a gap in the literature with regards these outcomes.

The majority of studies were industry-funded (n = 88; 70 percent), which can increase the chance of pro-industry findings.[166] Full disclosure of the nature and extent of industry involvement in the design, conduct, and analysis of such studies can help readers better evaluate the likelihood of industry bias in trial results. Of further note, funding was not disclosed for 19 percent of studies (n = 24), highlighting the need for transparency in reporting the nature and extent of financial support. Industry bias in the studies included in this review may include the choice of medication comparisons, dosages and outcomes being driven by the funder's interests and priorities. For instance, the largest volume of research within the report compared haloperidol with olanzapine or risperidone, whereas many other drugs have not been extensively examined.

The evidence is summarized by key question (KQ) in the sections that follow. Overall, there were few differences of clinical importance between the active drug comparisons. In general, few differences between FGAs and SGAs on symptom improvement were identified; however, we cannot assume that the drugs are equivalent. Rather, the analyses were unable to detect differences often as a result of small numbers of trials for any given comparison and outcome. Moreover, most of the trials were designed as superiority trials testing the a priori hypothesis that SGAs are more efficacious than FGAs; hence, the individual trials, and some of the pooled analyses, may not have adequate power to confirm equivalence. FGAs generally had poorer safety profiles during the studies' followup period.

Key Question 1: Core Illness Symptoms

The findings for core illness symptoms are presented for each condition in Table 106. Comparisons and outcomes for which there was insufficient strength of evidence (e.g., evidence from single trials) to draw a conclusion are not displayed in the tables. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following comparisons: chlorpormazine versus olanzapine, quetiapine, and ziprasidone; fluphenazine versus olanzapine, quetiapine, and risperidone; haloperidol versus asenapine; perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone; trifluoperazine versus clozapine.

For schizophrenia or schizophrenia-related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive, negative, or general psychopathology. Clozapine showed benefits for total score (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive or general psychopathology, global ratings, or total symptom score. The SoE was low for positive outcomes, global ratings and total scores; the SoE was insufficient for general psychopathology. Aripiprazole showed benefits for negative symptoms (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general psychopathology (low SoE). The findings were discordant for total symptom score: no difference was found based on Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) (low SoE), whereas one study showed benefits for clozapine on the Clinical Global Impression–Improvement (CGI–I) and Severity (CGI–S) scales (insufficient SoE).

Twenty-seven studies provided data on core illness symptoms for haloperidol versus olanzapine. No differences were found for positive symptoms (low SoE). Olanzapine was favored for negative symptoms (moderate SoE). In terms of general psychopathology, a significant benefit for olanzapine was found based on the Hamilton Rating Scale for Depression (HAM–D), Montgomery-Asberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS). No differences were observed for the other five scales of general symptoms assessed. The SoE varied across outcomes from insufficient to moderate. Olanzapine was favored for global ratings and total symptom scores based on the CGI–S and PANSS; however no differences were found for the other four scales assessed. The SoE for these outcomes also varied from insufficient to moderate.

Nine studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive, negative, or general psychopathology. A significant difference favoring haloperidol was found for one (CGI–S) of the five global ratings and total symptom scores assessed. The SoE across outcomes ranged from insufficient to moderate.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. There were no differences for positive symptoms (low SoE). Risperidone was favored for negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS) and PANSS (negative) (moderate SoE). No differences were found for any of the six measures used to assess general psychopathology (low or insufficient SoE). Seven of the global ratings or total symptom scores showed no differences, whereas the Symptom Checklist (SCL–90–R) showed a benefit for risperidone (low or insufficient SoE).

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms, general psychopathology, global ratings, or total score (low or insufficient SoE). No studies provided data on positive symptoms.

A total of 11 studies examined patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (four RCTs). No significant differences were found for mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low or insufficient). Two studies compared haloperidol versus olanzapine and found no significant differences in sleep, mood (mania), mood (depression), global ratings, or total symptom scores (low or insufficient SoE). Two studies compared haloperidol with aripiprazole and found no differences in mood (mania), mood (depression), positive or negative symptoms, or global ratings and total symptom scores (low or insufficient SoE). Single studies compared chlorpromazine versus clozapine and haloperidol versus quetiapine and ziprasidone (insufficient SoE).

Table 106. Summary of the strength of evidence for core illness symptoms (KQ1)

Outcome	Comparison (Number of Studies)	SoE	Summary
Schizophrenia and Schizophrenia-Related Psychoses			
Positive Symptoms	Haloperidol vs. aripiprazole	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No differences in PANSS (14 RCTs) or SAPS (2 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No difference for PANSS (20 RCTs) or SAPS (2 RCTs).
Negative Symptoms	Haloperidol vs. aripiprazole	Moderate	Significant difference favoring aripiprazole for PANSS (3 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs) and SANS (2 RCTs).
	Haloperidol vs. olanzapine	Moderate	Significant difference favoring olanzapine for PANSS (14 RCTs) and SANS (5 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Moderate	Significant difference favoring risperidone for PANSS (moderate SoE, 20 RCTs) and SANS (moderate SoE, 4 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for PANSS (2 RCTs).
General Psycho-pathology	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for HAM–D (moderate SoE, 3 RCTs) and MADRS (moderate SoE, 6 RCTs). No difference for ABS (low SoE, 2 RCTs), ACES (low SoE, 2 RCTs), CDS–S (low SoE, 3 RCTs), HAM–A (low SoE, 2 RCTs), and PANSS (low SoE, 10 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for CDS–S (2 RCTs) or PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No significant differences for CDS–S (3 RCTs), HAM–D (2 RCTs), PANSS (13 RCTs), and YMRS (2 RCTs).
Global Ratings and Total Scores	Chlorpromazine vs. clozapine	Moderate	Significant difference favoring clozapine for BPRS (6 RCTs).
	Haloperidol vs. aripiprazole	Low	No significant difference for BPRS (3 RCTs) and CGI–S (5 RCTs).
	Haloperidol vs. clozapine	Low	No differences for BPRS (4 RCTs) and PANSS (3 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for CGI–S (moderate SoE, 7 RCTs) and PANSS (moderate SoE, 14 RCTs). No difference for BPRS (low SoE, 13 RCTs) or CGI–I (low SoE, 2 RCTs).

Table 106. Summary of the strength of evidence for core illness symptoms (KQ1) (continued)

Outcome	Comparison (Number of Studies)	SoE	Summary
Schizophrenia and Schizophrenia-Related Psychoses (continued)			
Global Ratings and Total Scores (continued)	Haloperidol vs. quetiapine	Low to moderate	Significant difference favoring haloperidol for CGI–S (moderate SoE, 4 RCTs). No differences for BPRS (low SoE, 4 RCTs), CGI–I (low SoE, 3 RCTs), or PANSS (low SoE, 6 RCTs).
	Haloperidol vs. risperidone	Low	No difference for BPRS (13 RCTs), CGI–I (3 RCTs), CGI–S (8 RCTs), PANSS (20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for BPRS (4 RCTs), CGI–S (4 RCTs), GAF (3 RCTs), and PANSS (4 RCTs).
Bipolar Disorder			
Mood (mania)	Haloperidol vs. aripiprazole	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No significant difference in YMRS (2 RCT).
	Haloperidol vs. risperidone	Low	No significant difference in YMRS (3 RCTs).
Mood (depression)	Haloperidol vs. aripiprazole	Low	No significant difference in MADRS (2 RCTs).
Global Ratings and Total Scores	Haloperidol vs. aripiprazole	Low	No significant difference in CGI–BP (2 RCTs).

ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–BP = Clinical Global Impression–Bipolar; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; YMRS = Young Mania Rating Scale

Key Question 2: Functional Outcomes and Health Care Resource Utilization

The findings for functional outcomes and health care system utilization are presented for each condition and comparison in Table 107. We did not assess the SoE for outcomes in KQ2.

Results for functional outcomes were available from 9 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. No significant differences in functional outcomes were observed between groups for most of the comparisons. However, in most cases evidence came from single studies. Results for health care system utilization were available for 10 head-to-head comparisons, and no differences were found for any comparison.

Only one trial comparing haloperidol with olanzapine provided data on functional outcomes in patients with bipolar disorder. Significant differences were found favoring olanzapine for the number of individuals actively working for pay. No differences were found for household or work activities impairment.

Table 107. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2)

Outcome	Comparison	Summary (number of studies)
Schizophrenia and Schizophrenia-Related Psychoses		
Functional Outcomes	Fluphenazine vs. quetiapine	No significant differences for sexual dysfunction or improvement on treatment (1 RCT).
	Fluphenazine vs. risperidone	No significant differences for sexual dysfunction or improvement on treatment (1 RCT).
	Haloperidol vs. olanzapine	No significant difference for positive urine toxicology (1 RCT) or sexual dysfunction (1 RCT).
	Haloperidol vs. quetiapine	No significant difference for sexual dysfunction (1 RCT).
	Haloperidol vs. risperidone	No significant differences for economic independence (1 RCT) or attitude regarding drugs (1 RCT).
	Haloperidol vs. ziprasidone	No differences for sexual dysfunction (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. risperidone	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in patients with paid employment (1 RCT).
Health Care System Use	Chlorpromazine vs. clozapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. clozapine	No significant difference in mean hospital bed days (1 RCT).
	Haloperidol vs. olanzapine	No significant difference in mean hospital bed days or rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (3 RCTs).
	Haloperidol vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (2 RCTs).
	Perphenazine vs. olanzapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine	Significant difference favoring olanzapine for number of active workers (i.e., working for pay) (1 RCT). No difference in household or work activities impairment (1 RCT).

KQ = Key Question; RCT = randomized controlled trial

Key Question 3: Medication-Associated Adverse Events and Safety

The findings for the AEs that were deemed most clinically important are summarized in Table 108. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone), mortality (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. risperidone; thioridazine vs. clozapine and risperidone), diabetes mellitus (haloperidol vs. olanzapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone), and metabolic syndrome

(haloperidol vs. clozapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone).

Two trials each provided data on mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole; no significant differences were found, although the length of followup of the trials for the latter comparison was only 24 hours. For metabolic syndrome, two trials provided data for haloperidol versus olanzapine and showed no significant difference in incidence of metabolic syndrome. The SoE for these comparisons was low, suggesting that further research may change the results and change our confidence in the results.

Data were also recorded for general measures of adverse events (AEs) and specific AEs by physiological system (e.g., cardiovascular, endocrine); these outcomes were not assessed for SoE. For general measures of AEs, significant differences were found in the incidence of patients with AEs and withdrawals due to AEs for several comparisons. Most often, the comparison included haloperidol, and the risk was consistently higher for the FGA. The most frequently reported AEs with significant differences were in the category of extrapyramidal symptoms (EPS) and most often involved a comparison with haloperidol. In the vast majority of cases, the SGA had the preferred AE profile for EPS.

We were unable to adequately examine persistence and reversibility of AEs due to the relatively short followup of the included studies: study followup periods averaged 8 weeks. It is unclear whether AE persistence and reversibility of several significant AEs could be reasonably examined during this time period (e.g., metabolic conditions, body mass index or weight, and cardiovascular).

Table 108. Summary of the strength of evidence for medication-associated adverse events and safety (KQ3)

Adverse Event	Comparison	SoE	Summary (Number of Studies)
Mortality	Chlorpromazine vs. clozapine	Low	No significant difference (2 RCTs) (length of followup: 52 and 208 wks)
	Haloperidol vs. aripiprazole	Low	No significant difference (2 RCTs) (length of followup: 24 hrs for both)
Metabolic Syndrome	Haloperidol vs. olanzapine	Low	No significant difference (2 RCTs) (length of followup: 6 and 12 wks)

Hrs = hours; KQ = Key Question; RCT = randomized controlled trial; SoE = strength of evidence; wks = weeks; vs. = versus

Key Question 4: Other Outcomes

The findings for other outcomes are presented for each condition and comparison in Table 109. We did not assess the SoE for outcomes in KQ4.

Results for other outcomes were available for 19 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. Few significant differences were found across the comparisons and outcomes examined. For most significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials). Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (1 trial) and patient satisfaction (1 trial). Risperidone was favored over haloperidol for relapse rates (6 trials). Olanzapine was favored over perphenazine for time to all-cause medication discontinuation (1 trial). Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each); olanzapine, quetiapine,

risperidone, and ziprasidone (1 trial each). There was a significant difference in HRQoL for perphenazine over aripiprazole (1 trial).

Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder. Significant differences were found for health-related quality of life in one trial comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score, and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.

Table 109. Summary of the evidence for other outcomes (KQ4)

Comparison (Number of Studies)	Summary
Schizophrenia and Schizophrenia-Related Psychoses	
Chlorpromazine vs. clozapine	Significant difference favoring clozapine for response rates (3 RCTs). No difference in remission rates (2 RCTs).
Chlorpromazine vs. olanzapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. quetiapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. ziprasidone	No significant difference in response rates (1 RCT).
Fluphenazine vs. olanzapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. quetiapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. risperidone	No significant difference in response rates (1 RCT).
Haloperidol vs. aripiprazole	No significant difference in response rates (5 RCTs) or medication adherence (1 RCT). Difference favoring aripiprazole for caregiver and patient satisfaction (1 RCT).
Haloperidol vs. asenapine	No significant difference in response rates (1 RCT).
Haloperidol vs. clozapine	No significant difference in relapse (1 RCT), response (2 RCTs) or remission (1 RCT) rates, or patient satisfaction (1 RCT).
Haloperidol vs. olanzapine	Significant difference favoring olanzapine for response rates (14 RCTs) and remission rates (3 RCTs). No significant difference in medication adherence (1 RCT), patient insight into illness (1 RCT), or HRQoL (5 RCTs).
Haloperidol vs. quetiapine	No significant difference in response rates (6 RCTs), remission rates (1 RCT), or HRQoL (1 RCT).
Haloperidol vs. risperidone	Significant difference favoring risperidone for relapse rates (6 RCTs). No significant differences in remission rates (2 RCTs), response rates (16 RCTs), medication adherence (3 RCTs), patient satisfaction (1 RCT), or HRQoL (2 RCTs).
Haloperidol vs. ziprasidone	No significant difference in response rates (6 RCTs), remission rates (3 RCTs), or HRQoL (2 RCT).
Perphenazine vs. aripiprazole	No significant difference in response rates (1 RCT). Significant difference in HRQoL favoring perphenazine (1 RCT).
Perphenazine vs. olanzapine	No significant difference in HRQoL (1 RCT). Significant difference favoring olanzapine for time to all-cause medication discontinuation (1 RCT).
Perphenazine vs. quetiapine	No significant difference in HRQoL (1 RCT).
Perphenazine vs. risperidone	No significant difference in time to all-cause medication discontinuation (1 RCTs) and HRQoL (1 RCT).
Perphenazine vs. ziprasidone	No significant difference in HRQoL (1 RCT).

Table 109. Summary of the evidence for other outcomes (KQ4) (continued)

Comparison (Number of Studies)	Summary
Bipolar Disorder	
Haloperidol vs. aripiprazole	Significant difference in favor of haloperidol for relapse rates (1 RCT). No difference in remission (1 RCT) or response (2 RCTs) rates.
Haloperidol vs. olanzapine	No difference for relapse (1 RCT), response (1 RCT), or remission rates (1 RCT). Significant difference favoring haloperidol for HRQoL mental summary score (1 RCT). Significant difference favoring olanzapine for HRQoL physical summary score (1 RCT).
Haloperidol vs. quetiapine	No significant difference in response or remission rates (1 RCT).
Schizophrenia and Schizophrenia-Related Psychoses	
Haloperidol vs. risperidone	No difference in response rates (1 RCT).
Haloperidol vs. ziprasidone	Significant difference favoring haloperidol for response rates (1 RCT). No difference for remission rates (1 RCT).

KQ = Key Question; HRQoL = health-related quality of life; RCT = randomized controlled trial

Key Question 5: Subgroups

A total of 41 studies compared outcomes for predefined subgroups. Among the studies of patients with schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance. The race most often examined was Asian. No notable differences were observed for the subgroups compared to the overall findings.

The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar I and bipolar II. The results were consistent with the overall findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.

Results in the Context of Previous Literature

The results of this review are similar in some respects to another recent systematic review of SGAs versus FGAs, although the present review is broader in scope in terms of medications included, patient populations, and outcomes.[6] There were a number of methodological differences between the previous review and this one; the previous review included non-FDA-approved antipsychotics, restricted the analysis to only double-blinded trials, included only studies examining optimum SGA dosage and oral route of administration, and pooled data across efficacy outcome measures. The differences in the methodologies may have led to slightly different conclusions regarding individual SGAs.

The previous review compared nine SGAs (six of which were included in this report) with FGAs for overall efficacy (total symptom scores), positive, negative, and depressive symptoms, relapse, quality of life, EPS, weight gain, and sedation. They reported that the overall efficacy of the FDA-approved SGAs clozapine, olanzapine, and risperidone faired better than FGAs. In terms of global ratings and total symptom scores, we found that clozapine was more efficacious than chlorpromazine, but not compared with haloperidol. We found that olanzapine performed better than haloperidol on one of the three total symptom scores assessed. We found no differences between haloperidol and risperidone for the five total symptom scores reported. The previous review found that SGAs were not superior to FGAs regarding the negative symptoms. We found no difference in negative symptoms for haloperidol versus clozapine; however, we found evidence that olanzapine was more efficacious than haloperidol for negative symptoms, whereas the evidence for risperidone compared with haloperidol was mixed. In general, the

findings for AEs were consistent between reviews showing poorer safety profiles with respect to EPS for FGAs (specifically haloperidol) and more weight gain among the SGAs (in particular, olanzapine and risperidone).

The general results of our review for schizophrenia are consistent with the results of two widely cited trials in this clinical field: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[23] and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS).[21] The CATIE trial was included in this review and was designed to evaluate whether FGAs were inferior to SGAs in efficacy and safety. Findings from the CATIE trial suggested that the FGA perphenazine and various SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) differed more in their side-effect profiles than therapeutic effects. The study, like this review, also demonstrated that effectiveness across medications varied, and in some cases, this difference was clinically important. For example, in CATIE, clozapine was most effective for patients whose symptoms did not improve with first-line treatment, but it had a worse side-effect profile, and quetiapine (SGA) was more effective for patients who did not tolerate perphenazine (FGA). The CUtLASS trial was not included in our review as this trial compared FGAs and SGAs as classes rather than as individual medications. However, this study like CATIE and our review found that differences between 13 grouped FGAs and four grouped SGAs for effectiveness were not significantly different. This body of work suggests that there are no clear-cut advantages of either medication class, and that there is a range of medication choice (both FGA and SGA) for prescribing clinicians and their patients to consider during treatment initiation and maintenance. Establishing how to use existing medications safely and effectively to optimize patient outcomes, and determining the role and effect of long-term antipsychotic use (> 2 years) remains urgently needed both for treating schizophrenia and use of antipsychotics for bipolar disorder.

In general, there were some differences between this review and the above-cited studies with respect to methods and scope. Our review was very broad in scope, including all patient populations and all FDA-approved medications, regardless of dose or route of administration. We also included an exhaustive list of outcomes. The extent of outcomes we examined was substantial; however, many outcomes were reported too sparsely to provide strong evidence. Moreover, one of the contributions of this comprehensive synthesis is that it highlights this problem of variable outcome selection across trials while providing extensive details to consider when making treatment choices on an individual basis. One of the unique features of our review was the SoE assessments. Although previous trials and reviews have found some significant findings, our SoE assessments provide information on how confident we can be in those results and how likely the effects may change with future research. In most cases, the SoE was insufficient or low, highlighting the likelihood that future research may change the estimates of effect and the need for a stronger evidence base to inform clinical practice.

Applicability

This report included studies that compared an individual FGA to an individual SGA. Placebo-controlled studies or studies comparing a FGA versus another FGA, or a SGA versus another SGA, were not included. Therefore, the evidence is focused on the comparative effectiveness of FGAs versus SGAs, but not on their effectiveness and safety compared to placebo or other active agents. Overall, there were 22 head-to-head comparisons across the relevant studies; however, within most comparisons there were few studies.

The focus of this review was adults, age 18 to 64 years, with schizophrenia or schizophrenia-related psychoses and bipolar disorder. The average age across studies ranged from 21 to 50 years (median = 37 years [interquartile range (IQR), 33 to 41]). Most studies were highly selective in patient enrollment and included patients who (1) met strict diagnostic criteria for case definition, (2) had few comorbidities, and (3) used few or no concomitant medications. Older adults and the most seriously ill patients were also underrepresented. Such highly selective criteria may increase the likelihood of drug benefit and decrease the likelihood of AE occurrence. Almost half the studies involved hospitalized patients (inpatient treatment) (62 of 125 studies) or mixed inpatient and outpatient populations (26 studies); relatively few studies examined only outpatient treatment populations (19 studies). As such we judge the results of this report to be applicable to patients in outpatient and inpatient treatment settings.

Another factor that restricts the applicability of results is the limited duration of followup. The limited long-term (≥2 years) followup data precludes the ability to detect serious adverse events (SAEs) that may develop over the course of several years. The average length of followup in the included studies was only 8 weeks (IQR, 6 to 26 weeks). Further, a priori, we defined the following key AEs: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. In order to identify evidence for these important outcomes, we expanded our scope to search for and include cohort studies with a minimum 2-year duration. Despite a comprehensive search, we only identified two cohort studies meeting our criteria. This is an important limitation that needs to be considered when interpreting the results and applying them in clinical practice.

Limitation of Existing Evidence

Inconsistency in treatment comparisons, outcomes, outcome measurement, and patient populations across studies makes drawing firm clinical conclusions difficult. Few studies compared the same antipsychotic medications and dosage using similar measures; various scales and surrogate measures were used to assess efficacy for different outcomes and AEs. Consensus is needed regarding outcomes and measures used to assess outcomes. Surrogate outcome measures may have been attractive alternatives in studies given their ability to save time (e.g., shorter followup durations) and ease to assess. However, their main limitation may be the lack of correlation between the results from surrogate and clinically meanful outcomes. This inconsistency can lead to recommendations of harmful medications or the exclusion of beneficial medications. Examples of surrogate outcome measures in this report include laboratory values to indicate treatment emergent metabolic syndrome, a clinical outcome. Additionally, functional outcomes and symptomatic outcomes (e.g., sedation, restlessness) were rarely and unequally reported throughout the trial reports, even though these outcomes are often vital to patient compliance.

A key limitation and challenge in synthesizing and interpreting this body of evidence is the heterogeneous patient populations across and within studies, which is in part driven by the complex nature of these disorders and their course over time. The studies we included had very mixed populations with respect to disorder subtypes, comorbid drug/ or alcohol use, treatment resistance, and number of previous episodes. These variables may create differential response to treatment, and this has been the basis for recommendations around personalized medicine in this area.[167] We conducted extensive subgroup and sensitivity analyses to explore these varying features. In many cases, the subgroup analyses were consistent with the overall estimates of effect. In cases where some differences were found, these were often based on small numbers of studies within the subgroups. In any case, the results of subgroup analyses should be interpreted

as hypothesis generating rather than hypothesis confirming. Our findings may provide some information to make treatment decisions for individual patients, but need to be confirmed in future research. Moreover, treatment decisions and future research should take into consideration individual characteristics that can influence response to treatment including needs, preferences, past treatment history and response to previous medications, and clinical factors such as family history of medical conditions (e.g., diabetes, hypertension). Patients should have access to a range of options that meet their differing needs and response patterns, as well as changes in these over time.

An additional limitation and challenge of synthesis in this area is that characteristics of the research may have changed over time, including drug doses and patient populations. For instance, relatively higher doses of haloperidol may have been used in earlier studies. Further, patients in more recent studies may not have been exposed to an FGA, whereas in earlier studies patients may have been exposed, and have become resistant, to an FGA. An additional problem is that patient response to treatment may vary depending on what medication they were taking prior to entering the study.[23] Information on baseline medication was not often provided in the individual studies; this information should be collected and reported in future studies for clinicians who are reviewing study findings and should be acknowledged when considering treatment options for individual patients.

Another important limitation in this body of evidence pertains to the instruments used to measure outcomes. Over 100 different scales and subscales or composite outcomes were used to assess efficacy outcomes across the studies. Although some outcomes and scales were assessed fairly consistently for core symptoms across conditions, such as the PANSS and BPRS for schizophrenia, measurement of core symptoms using subscale scores, different criteria, and different measures were common. The CGI reported across the studies make study outcomes relevant for clinicians; however, the heterogeneity in the different types of scales used to measure global improvements makes comparisons of patient improvement across studies and interventions challenging.

We also identified a vast array of different measures to assess functional capacity. For instance, 80 different measures were used among studies comparing haloperidol with olanzapine. For most measures, only single trials provided data. This is problematic in that when significant differences are found, we are not able to discern whether they are real differences or arise due to multiple statistical testing. Discussion and consensus are also needed on outcomes that can provide more information on patient functioning and well-being. This includes a systematic assessment of outcomes potentially important to patients, such as health-related quality of life, social and occupational functioning, and legal interactions.

An important limitation of this review and other systematic reviews is the design and quality of the primary included studies. The majority of studies providing data for this report were RCTs (n = 123); however, most were designed as superiority trials, often with an a priori hypothesis that the SGA would be more efficacious.[25] The individual studies and, in many cases, the pooled results may not have had sufficient power to detect equivalence or noninferiority between drugs. These study designs are consistent with CATIE superiority trial design, but given the well-regarded results of CATIE and the findings from this review and others,[6] future trials need sound rationale for designing superiority trials versus using equivalence or inferiority designs. On another note, we assessed risk of bias in RCTs using an empirically derived tool developed by The Cochrane Collaboration and assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale. All of the trials had an unclear risk of bias (n = 78; 63 percent) or high

risk of bias (n = 45; 37 percent). Only 15 RCTs (12 percent) were evaluated as having adequately generated the allocation sequence, and 6 RCTs (5 percent) had an adequately concealed allocation processes. Measures employed by the study investigators to ensure that the allocation sequence was random and occurred without foreknowledge of treatment assignments was unclear in the majority of the trials. These features should be routinely employed in order to avoid selection bias.

Only 17 percent of RCTs (n = 20) reported blinding study investigators and participants (26 percent had unclear reporting), which is another important limitation of this body of evidence as a lack of blinding has been shown to produce exaggerated treatment effects.[6] Blinding through use of matched placebo tablets that appear and taste similar to the study medication may reduce the risk that the knowledge of which intervention was received, rather than the active drug itself, affected outcomes. Studies should also consistently ensure and report that outcome assessors are blinded to treatment allocation. Incomplete outcome data was a limitation in almost half of the trials (unclear risk of bias, 26 percent; high risk of bias, 20 percent) due to loss to followup and inadequate handling of missing data in the reporting and analysis, which may have exaggerated reported treatment effects. The majority of trials were free of selective reporting (97 percent) and other sources of bias (e.g., significant baseline imbalances between study groups) (84 percent).

Two cohort studies were included in this review, due to their focus on AEs (tardive dyskinesia and mortality rates). These studies were identified as being good quality cohorts, receiving a rating of 8 out of 9 points on the Newcastle-Ottawa Scale. However, these cohort studies are limited by their design; the lack of randomization for treatment allocation makes the results vulnerable to bias due to a lack of comparability between treatment groups.

With regards to bipolar disorder, none of the included studies was limited to individuals with bipolar depression and therefore no conclusions can be made about the comparative effectiveness of interventions for this condition.

This comparative effectiveness review (CER) has several limitations. Only English-language studies were eligible for inclusion in the review; therefore, it is possible that relevant studies published in other languages may have affected the review findings although. However, our findings are consistent with a similar review that included non-English studies.[6] The scope of this report was limited to the direct comparison of individual FGAs with individual SGAs. Although this produces results that are internally valid, there is a risk that findings of no difference lead to false conclusions of equal efficacy by the reader. Future research incorporating indirect analyses through mixed treatment comparisons may add more strength to the evidence base. Further, we cannot make conclusions on the comparison of antipsychotics within the same drug class or with placebo. Therefore, without formal indirect quantitative or qualitative comparisons, no conclusions can be made as to the comparative efficacy of drugs in the same class. In addition, evidence on the use of other drug classes (e.g., anticonvulsants) that are frequently used in the treatment of these patient populations is not considered in this report. Finally, specific patient populations (e.g., patients with prior antipsychotic resistance) were under-studied in long-term trials, precluding firm conclusions relating to comparative effectiveness, response and remission rates, and side-effects profiles. The inclusion criteria of many studies were highly selective, primarily examining inpatients with no serious mental illness and who were not alcohol or substance users. This may not be generally reflective of patients with schizophrenia, as there is a high prevalence of comorbid disorders and alcohol or illicit drug use in this patient population.

This report presents a synthesis of the available evidence on the effectiveness and safety of antipsychotics in the adult population. However, we do not make clinical recommendations on the use of these medications, as this is the purview of the user group. We trust that the evidence presented in this report will be helpful in the further development of clinical practice guidelines in this field.

Future Research

This review identified a growing body of literature examining the effectiveness of FGAs and SGAs for treating schizophrenia and related psychoses. However, for many of the individual comparisons there were few trials. There is a need for consensus on the most important FGA and SGA comparisons. For many of the comparisons, the FGA was haloperidol. As haloperidol is known to have a poor AE profile, using this as the standard comparison may exaggerate the apparent safety profile of the SGA being compared. Consensus is needed on which comparisons will be the most informative and provide the most valid and accurate information to inform clinical decisions.

For treating bipolar disorder, more head-to-head trials are needed to compare the effectiveness of currently approved FGAs and SGAs. Given that antipsychotic medications are used to augment treatment with mood-stabilizing medications to ensure effective treatment of core illness symptoms for various forms of the disorder (e.g., acute mania, bipolar depression) and maintenance treatment, further research is necessary to better understand the impact of treatment on patient safety and function.

More longitudinal research is also needed on long-term AEs. Only two cohort studies were identified for this review that examined SAEs with long-term antipsychotic use; however, these studies only provided evidence for two SAEs: tardive dyskinesia and mortality rates. Studies examining the naturalistic and long-term efficacy and, particularly, the safety of antipsychotics over the course of several years and across a number of important AEs are required. Such studies could be modeled after longitudinal cohort studies in other fields, such as the Framingham study[168] that has been ongoing for decades to examine risk factors for cardiovascular disease.

Short- and long-term evaluations of the effectiveness of FGAs and SGAs with patient subpopulations, including patients with medical and neurological comorbidities, are needed. Further, there is a need for studies investigating how drug dose, age, and other factors, such as comorbidities, influence the occurrence of SAEs, which would help estimate possible risks in specific patient populations.

Future studies should examine functional naturalistic outcomes that are important to patients. These outcomes include health-related quality of life and other patient-reported outcomes, relationships, academic and occupational performance, and legal interactions.

Conclusions

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness and safety of individual FDA-approved FGAs compared with individual FDA-approved SGAs. The report provides extensive details in terms of study characteristics and methodological features, which may help inform individual treatment decisions. The focus of the report was adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. The vast majority of relevant studies involved patients with schizophrenia or schizophrenia-related psychoses. Studies most often involved haloperidol, which was compared most frequently with risperidone (43 studies) and olanzapine (37 studies). Numerous studies

provided data on core illness symptoms; however, many different scales were used to assess outcomes, which limited the quantitative pooling of data. Few notable differences of clinical importance were identified. In the majority of cases where significant differences were observed, the SGA showed greater improvement in core illness symptoms. Further, the SoE was low or insufficient for most comparisons, suggesting that future research may change the results and change our confidence in the results.

Data on the relative effectiveness of individual FGAs and SGAs for functional outcomes, health care system utilization, and other outcomes were generally sparse. Numerous tasks and tests were used to assess functional capacity. In most cases, only single studies contributed to each measure. The variety of functional measures assessed across studies precluded firm conclusions regarding the overall effectiveness of individual drugs in terms of patient functioning. Few studies reported on health care system utilization or patient-important outcomes. Where health-related quality of life was assessed, no differences were found.

The scope of this report included cohort studies with a minimum followup of 2 years in order to identify AEs of most clinical importance, including diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. Only two studies with long-term followup were identified; hence, evidence on these important AEs is limited and urgently needed. A variety of AEs associated with numerous physiological systems were reported. The AEs most often reported involved EPS, which occurred more frequently for FGAs, particularly haloperidol, than for SGAs.

The evidence for important subgroups was limited. The most frequently examined subgroups were race and treatment resistance. There were no notable differences in outcomes for these subgroups compared to the overall results.

Future research needs to incorporate design elements to minimize bias, in particular blinding of investigators, patients, and outcome assessors and adequate handling and reporting of missing data. Researchers need to ensure and report on appropriate methods for sequence generation and allocation concealment. Long-term longitudinal studies of at least 2-year duration are needed to detect important differences in the relative safety profile of individual FGAs and SGAs.

In summary, data on the comparative effectiveness of individual FGAs and SGAs precluded drawing firm conclusions for outcomes that are directly relevant to front-line clinical decisions. Overall, there were few statistically significant differences. Outcomes potentially important to patients were rarely assessed. Finally, data on long-term safety are lacking and urgently needed.

References

1. Meltzer HY, Huang M. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res. 2008;172:177-97. PMID:18772033
2. Lopez-Gil X, Artigas F, Adell A. Unraveling monoamine receptors involved in the action of typical and atypical antipsychotics on glutamatergic and serotonergic transmission in prefrontal cortex. Curr Pharm Des. 2010;16(5):502-15. PMID:19909228
3. Wang CC, Farley JF. Patterns and predictors of antipsychotic medication use among the U.S. population: Findings from the Medical Expenditure Panel Survey. Res Social Adm Pharm. 2009. PMID:21272525
4. Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. Pharmacoepidemiol Drug Saf. 2011;20(2):177-84. PMID:21254289
5. Ascher-Svanum H, Nyhuis AW, Stauffer V, et al. Reasons for discontinuation and continuation of antipsychotics in the treatment of schizophrenia from patient and clinician perspectives. Curr Med Res Opin. 2010;26(10):2403-10. PMID:20812791
6. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31-41. PMID:19058842
7. McDonagh M, Peterson K, Carson S, et al. Drug Class Review: Atypical Antipsychotic Drugs: Final Update 3 Report [Internet]. Portland (OR): Oregon Health & Science University; 2010 Jul Drug Class Reviews. 2010. PMID:21348048
8. Maglione M, Maher AR, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Sep Report No: 11-EHC087-EF AHRQ Comparative Effectiveness Reviews 2011. PMID:22132426
9. Seida JC, Schouten R, Mousavi SS, et al. First- and Second-Generation Antipsychotics for Children and Young Adults. Comparative Effectiveness Review No 39 (Prepared by the University of Alberta Evidence-based Practice Center under Contract No 290-2007-10021) AHRQ Publication No 11-EHC077 Rockville, MD Agency for Healthcare Research and Quality 2011.
10. American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision ed. Washington, D.C.: American Psychiatric Association; 2000.
11. Bhugra D. The global prevalence of schizophrenia. PLoS Med. 2005;2(5):e151. PMID:15916460
12. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Arlington (VA). American Psychiatric Association; 2004.
13. Carlsson A. Antipsychotic drugs, neurotransmitters, and schizophrenia. Am J Psychiatry. 1978;135(2):165-73. PMID:23684
14. Nikam SS, Awasthi AK. Evolution of schizophrenia drugs: a focus on dopaminergic systems. Curr Opin Investig Drugs. 2008;9(1):37-46. PMID: 18183530
15. Campbell M, Young PI, Bateman DN, et al. The use of atypical antipsychotics in the management of schizophrenia. Br J Clin Pharmacol. 1999;47(1):13-22. PMID:10073734
16. Bishara D, Taylor D. Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. Drugs. 2008;68(16):2269-92. PMID:18973393
17. Kane J. Commentary: consensus statement on negative symptoms. Schizophr Bull. 2006;32(2):223-4. PMID:16221996
18. Miyamoto S, Duncan GE, Mailman RB, et al. Developing novel antipsychotic drugs: strategies and goals. Curr Opin CPNS Invest Drugs. 2000;2:25-39.

19. Dawkins K, Lieberman JA, Lebowitz BD, et al. Antipsychotics: Past and Future: National Institute of Mental Health Division of Services and Intervention Research Workshop, July 14, 1998. Schizophr Bull. 1999;25(2):395-405. PMID:10416740

20. Murphy BP, Chung YC, Park TW, et al. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res. 2006;88(1-3):5-25. PMID:16930948

21. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second vs. first generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63(10):1079-87. PMID:17015810

22. Lewis SW, Barnes TR, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006;32(4):715-23. PMID:16540702

23. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;(12):1209-23. PMID:16172203

24. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600-10. PMID:16585434

25. Lieberman JA, Stroup TS. The NIMH-CATIE Schizophrenia Study: what did we learn? Am J Psychiatry. 2011;168(8):770-5. PMID:121813492

26. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry. 2002;159(4 Suppl):1-50. PMID:11958165

27. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The Cochrane Collaboration; 2008.

28. Eden J, Levit L, Berg A, Morton S, eds. Finding what works in health care : standards for systematic reviews / Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Board on Health Care Services, Institute of Medicine of the National Academies. Institute of Medicine of the National Academies. The National Academies Press; 2011.

29. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet. 1997;350(9072):185-6. PMID:9250191

30. Wells G, Shea B, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Dept of Epidemiology & Community Medicine, University of Ottawa, Canada. 2009. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

31. Tran-Johnson TK, Sack DA, Marcus RN, et al. Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2007;68(1):111-9. PMID:17284138

32. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry. 2005;187:235-42. PMID:16135860

33. Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry. 2009;194(1):40-8. PMID:19118324

34. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. BMC Med Res Methodol. 2001;1:6. PMID:11459516

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. PMID:3802833

36. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet. 1998;351(9096):123-7. PMID:9439507

37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. PMID:12111919

38. Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. J Epidemiol. 2005;15(6):235-43. PMID:16276033

39. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2009. PMID:19595577

40. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. PMID:18436948

41. Gartlehner G, Hansen RA, Nissman D, Lohr KN, et al. Criteria for distinguishing effectiveness from efficacy trials in systematic reviews: Technical Review 12 (Prepared by the RTI-International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) AHRQ Publication No. 06-0046. Rockville, MD: Agency for Healthcare Research and Quality. April 2006.

42. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. PMID:19621072

43. Altamura AC, Velona I, Curreli R, et al. Is olanzapine better than haloperidol in resistant schizophrenia? A double-blind study in partial responders. Int J Psychiatr Clin Pract. 2002;6(2):107-11.

44. Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. Psychopharmacology (Berl). 2006;188(3):281-92. PMID:16953381

45. Apiquian R, Fresan A, Munoz-Delgado J, et al. Variations of rest, activity rhythm and sleep, wake in schizophrenic patients versus healthy subjects: an actigraphic comparative study. Biol Rhythm Res. 2008;39(1):69-78.

46. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry. 1997;42(4):233-46. PMID:9270900

47. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine is not associated with increase in prolactin secretion in contrast to haloperidol. Arch Med Res. 2002;33(6):562-5. PMID:12505103

48. Barbini B, Scherillo P, Benedetti F, et al. Response to clozapine in acute mania is more rapid than that of chlorpromazine. Int Clin Psychopharmacol. 1997;12(2):109-12. PMID:9219046

49. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacol. 1996;14(2):111-23. PMID:8822534

50. Beasley CM, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol. 1997;7(2):125-37. PMID:9169300

51. Bernardo M, Parellada E, Lomena F, et al. Double-blind olanzapine vs. haloperidol D2 dopamine receptor blockade in schizophrenic patients: a baseline-endpoint. Psychiatry Res. 2001;107(2):87-97. PMID:11530275

52. Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. J Clin Psychopharmacol. 1996;16(1):38-44. PMID:8834417

53. Borison RL, Pathiraja AP, Diamond BI, et al. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull. 1992;28(2):213-8. PMID:1381102

54. Boulay LJ, Labelle A, Bourget D, et al. Dissociating medication effects from learning and practice effects in a neurocognitive study of schizophrenia: olanzapine versus haloperidol. Cogn Neuropsych. 2007;12(4):322-38. PMID:17558641

55. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry. 1994;151(1):20-6. PMID:8267129

56. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Archives of General Psychiatry. 2002;59(5):441-8. PMID:11982448

57. Brook S, Walden J, Benattia I, et al. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl). 2005;178(4):514-23. PMID:15650846

58. Buchanan RW, Ball MP, Weiner E, et al. Olanzapine treatment of residual positive and negative symptoms. Am J Psychiatry. 2005;(1):124-9. PMID:15625210

59. Cavallaro R, Mistretta P, Cocchi F, et al. Differential efficacy of risperidone versus haloperidol in psychopathological subtypes of subchronic schizophrenia. Hum Psychopharmacol. 2001;16(6):439-48. PMID:12404552

60. Ceskova E, Svestka J. Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. Pharmacopsychiatry. 1993;26(4):121-4. PMID:7694306

61. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol. 1993;13(1):25-40. PMID:7683702

62. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv. 2001;52(11):1510-4. PMID:11684748

63. Claghorn J, Honigfeld G, Abuzzahab FS, Sr., et al. The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol. 1987;7(6):377-84. PMID:3323261

64. Claus A, Bollen J, De CH, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand. 1992;85(4):295-305. PMID:1375801

65. Glick ID, Marder SR. Long-term maintenance therapy with quetiapine versus haloperidol decanoate in patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2005;66(5):638-41. PMID:15889952

66. Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry. 1998;(7):914-20. PMID:9659857

67. Conley RR, Kelly DL, Nelson MW, et al. Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. Clin Neuropharmacol. 2005;28(4):163-8. PMID:16062094

68. Copolov DL, Link CG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. Psychol Med. 2000;30(1):95-105. PMID:10722180

69. Corripio I, Catafau AM, Perez V, et al. Striatal dopaminergic D2 receptor occupancy and clinical efficacy in psychosis exacerbation: a 123I–IBZM study with ziprasidone and haloperidol. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(1):91-6. PMID:15610950

70. Covington L, Cola PA. Clozapine vs. Haloperidol: antipsychotic effects on sexual function in schizophrenia. Sex Disabil. 2000;18(1):41-8.

71. Crespo-Facorro B, Perez-Iglesias R, Ramirez-Bonilla M, et al. A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. J Clin Psychiatry. 2006;67(10):1511-21. PMID:17107241

72. Csernansky JG, Mahmoud R, Brenner R, et al. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. New Engl J Med. 2002;346(1):16-22. PMID:11777998

73. McCue RE, Waheed R. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. Br J Psychiatry. 2006;40. PMID:17077434

74. Daniel DG, Currier GW, Zimbroff DL, et al. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. J Psychiatr Pract. 2007;13(3):170-7. PMID:17522560

75. Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am J Psychiatry. 2009;166(6):675-82. PMID:19369319

76. De Oliveira IR, Elkis H, Gattaz WF, et al. Aripiprazole for patients with schizophrenia and schizoaffective disorder: an open-label, randomized, study versus haloperidol. CNS Spectr. 2009;14(2):93-102. PMID:19238124

77. De Sena EP, Santos-Jesus R, Miranda-Scippa A, et al. Relapse in patients with schizophrenia: a comparison between risperidone and haloperidol. Rev Bras Psiquiatr. 2003;25(4):220-3. PMID:15328547

78. De Haan L, Van BM, Lavalaye J, et al. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry. 2003;160(2):303-9. PMID:12562577

79. Emsley RA, Raniwalla J. A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. Int Clin Psychopharmacol. 2000;15(3):121-31. PMID:10870870

80. Emsley R, Turner HJ, Schronen J, et al. Effects of quetiapine and haloperidol on body mass index and glycaemic control: a long-term, randomized, controlled trial. Int J Neuropsychopharmacol. 2005;8(2):175-82. PMID:15737251

81. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Schizophr Bull. 1999;25(4):721-9. PMID:10667742

82. Fakra E, Khalfa S, Da FD, et al. Effect of risperidone versus haloperidol on emotional responding in schizophrenic patients. Psychopharmacology (Berl). 2008;200(2):261-72. PMID:18575849

83. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol. 1998;18(4):296-304. PMID:9690695

84. Goldman MB, Hussain N. Absence of effect of olanzapine on primary polydipsia: results of a double-blind, randomized study. J Clin Psychopharmacol. 2004;24(6):678-80. PMID:15538138

85. Heck AH, Haffmans PM, de G, I, et al. Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double-blind, multi-center trial. Schizophr Res. 2000;46(2-3):97-105. PMID:11120421

86. Hirsch SR, Kissling W, Bauml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry. 2002;63(6):516-23. PMID:12088164

87. Hong CJ, Chen JY, Chiu HJ, et al. A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. Int Clin Psychopharmacol. 1997;12(3):123-30. PMID:9248867

88. Ishigooka J, Inada T, Miura S. Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. Psychiatry Clin Neurosci. 2001;55(4):403-14. PMID:11442893

89. Jakovljevic M. Olanzapine versus fluphenazine in the acute (6-week) treatment of schizophrenia. Psychiatr Danub. 1999;(1-2):3-11.

90. Janicak PG, Keck PE, Jr., Davis JM, et al. A double-blind, randomized, prospective evaluation of the efficacy and safety of risperidone versus haloperidol in the treatment of schizoaffective disorder. J Clin Psychopharmacol. 2001;21(4):360-8. PMID:11476119

91. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371(9618):1085-97. PMID:18374841

92. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2002;(9):763-71. PMID:12363115

93. Kane JM, McQuade RD, Marcus RN, et al. Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. J Clin Psychiatry. 2007;(2):213-23. PMID:17335319

94. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Archives of General Psychiatry. 1988;45(9):789-96. PMID:3046553

95. Kane JM, Marder SR, Schooler NR, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. Archives of General Psychiatry. 2001;58(10):965-72. PMID:11576036

96. Kane JM, Khanna S, Rajadhyaksha S, et al. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2006;21(1):21-8. PMID:16317313

97. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30(2):106-15. PMID:20520283

98. Kasper S, Lerman MN, McQuade RD, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol. 2003;(4):325-37. PMID:14609439

99. Kee KS, Kern RS, Marshall BD, Jr., et al. Risperidone versus haloperidol for perception of emotion in treatment-resistant schizophrenia: preliminary findings. Schizophr Res. 1998;31(2-3):159-65. PMID:9689720

100. Keefe RS, Poe MP, McEvoy JP, et al. Source monitoring improvement in patients with schizophrenia receiving antipsychotic medications. Psychopharmacology (Berl). 2003;169(3-4):383-9. PMID:12759802

101. Keefe RS, Young CA, Rock SL, et al. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res. 2006;81(1):1-15. PMID:16202565

102. Kim SH, Han DH, Joo SY, et al. The effect of dopamine partial agonists on the nicotine dependency in patients with schizophrenia. Hum Psychopharmacol. 2010;25(2):187-90. PMID:20033907

103. Klieser E, Strauss WH, Lemmer W. The tolerability and efficacy of the atypical neuroleptic remoxipride compared with clozapine and haloperidol in acute schizophrenia. Acta Psychiatr Scand Suppl. 1994;380:68-73. PMID:8048341

104. Kongsakon R, Trinidad-Onate P, Chaudhry HR, et al. Asian outpatients with schizophrenia: a double-blind randomized comparison of quality of life and clinical outcomes for patients treated with olanzapine or haloperidol. J Med Assoc Thailand. 2006;89(8):1157-70. PMID:17048425

105. Krakowski MI, Czobor P. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Archives of General Psychiatry. 2006;(6):622-9. PMID:16754835

106. Lahti AC, Weiler MA, Holcomb HH, et al. Modulation of limbic circuitry predicts treatment response to antipsychotic medication: a functional imaging study in schizophrenia. Neuropsychopharmacol. 2009;34(13):2675-90. PMID:19675535

107. Lee SM, Chou YH, Li MH, et al. Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(5):1101-7. PMID:17475386

108. Lieberman JA, Tollefson G. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry. 2003;(8):1396-404. PMID:12900300

109. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacol. 2003;28(5):995-1003. PMID:12700715

110. Lindenmayer JP, Khan A, Iskander A, et al. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J Clin Psychiatry. 2007;68(3):368-79. PMID:17388705

111. Liu SK, Chen WJ, Chang CJ, et al. Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: a trial of risperidone versus haloperidol. Neuropsychopharmacol. 2000;22(3):311-9. PMID:10693159

112. Ljubin T, Milas DZ, Mimica N, et al. A preliminary study of the comparative effects of olanzapine and fluphenazine on cognition in schizophrenic patients. Hum Psychopharmacol. 2000;15(7):513-9. PMID:12404620

113. Marder SR, Glynn SM, Wirshing WC, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. Am J Psychiatry. 2003;(8):1405-12. PMID:12900301

114. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry. 1994;151(6):825-35. PMID:7514366

115. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania: a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol. 2005;15(5):573-85. PMID:16139175

116. Miceli JJ, Tensfeldt TG, Shiovitz T, et al. Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder. Clin Ther. 2010;32(3):472-91. PMID:20399985

117. Min SK, Rhee CS, Kim CE, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic patients: a parallel group double-blind comparative trial. Yonsei Med J. 1993;34(2):179-90. PMID:7691017

118. Moller HJ, Riedel M, Jager M, et al. Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on schizophrenia. Int J Neuropsychopharmacol. 2008;11(7):985-97. PMID:18466670

119. Moreno RA, Hanna MM, Tavares SM, et al. A double-blind comparison of the effect of the antipsychotics haloperidol and olanzapine on sleep in mania. Braz J Med Biol Res. 2007;40(3):357-66. PMID:17334533

120. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry. 1995;166(6):712-26. PMID:7545060

121. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand. 1997;96(4):265-73. PMID:9350955

122. Potkin SG, Weiden PJ, Loebel AD, et al. Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. Int J Neuropsychopharmacol. 2009;12(9):1233-48. PMID:19419595

123. Purdon SE, Malla A. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci. 2001;(2):137-49. PMID:11291531

124. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psych. 2000;57(3):249-58. PMID:10711911

125. Remillard S, Pourcher E, Cohen H. Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. J Int Neuropsychol Soc. 2008;14(1):110-8. PMID:18078537

126. Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. New Engl J Med. 1997;337(12):809-15. PMID:9295240

127. Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA. 2003;290(20):2693-702. PMID:14645311

128. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry. 2002;159(7):1146-54. PMID:12091192

129. Saddichha S, Ameen S, Akhtar S. Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomized, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol. J Clin Psychopharmacol. 2008;(1):27-31. PMID:18204337

130. Sayers SL, Campbell EC, Kondrich J, et al. Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. J Nerv Ment Dis. 2005;193(6):379-86. PMID:15920378

131. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Treatment discontinuation following randomization to open-label olanzapine, risperidone or typical antipsychotics during a one-year treatment for schizophrenia. Clin Schizophr Relat Psychoses. 2008;2(3):226-34. PMID:15649317

132. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005;162(5):947-53. PMID:15863797

133. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol. 1998;21(3):176-80. PMID:9617509

134. Sergi MJ, Green MF, Widmark C, et al. Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. Am J Psychiatry. 2007;164(10):1585-92. PMID:17898351

135. Shrivastava A. Comparative study of risperidone and haloperidol on clinical and psychosocial parameters in treatment of schizophrenia: a randomised open trial. Indian J Pscychiatry. 2000;(1):52-6. PMID:21407908

136. Smelson DA, Ziedonis D, Williams J, et al. The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. J Clin Psychopharmacol. 2006;26(1):9-12. PMID:16415698

137. Smith RC, Infante M. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. Int J Neuropsychopharmacol. 2001;(3):239-50. PMID:11669086

138. Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol. 2005;15(1):75-84. PMID:15572276

139. Tamrakar SM, Nepal MK, Koirala NR, et al. An open, randomized, comparative study of efficacy and safety of risperidone and haloperidol in schizophrenia. Kathmandu Univ Med J. 2006;4(2):152-60. PMID:18603890

140. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. Archives of General Psychiatry. 2003;60(12):1218-26. PMID:14662554

141. Tollefson GD, Beasley CMJ, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: Results of an international collaborative trial. Am J Psychiatry. 1997;154(4):457-65. PMID:9090331

142. Alvarez-Jimenez M, Gonzalez-Blanch C, Vazquez-Barquero JL, et al. Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: a randomized controlled trial. J Clin Psychiatry. 2006;67(8):1253-60. PMID:16965204

143. Velligan DI, Newcomer J, Pultz J, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res. 2002;53(3):239-48. PMID:11738537

144. Vieta E, Ramey T, Keller D, et al. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. J Psychopharmacol. 2010;24(4):547-58. PMID:19074536

145. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry. 2002;159(2):255-62. PMID:11823268

146. Wirshing DA, Marshall BD, Jr., Green MF, et al. Risperidone in treatment-refractory schizophrenia. Am J Psychiatry. 1999;156(9):1374-9. PMID:10484947

147. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry. 2001;158(7):1149-51. PMID:11431240

148. Wynn JK, Green MF, Sprock J, et al. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophr Res. 2007;95(1-3):134-42. PMID:17662577

149. Yen YC, Lung FW, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(2):285-90. PMID:14751424

150. Zhang XY, Zhou DF, Cao LY, et al. Risperidone versus haloperidol in the treatment of acute exacerbations of chronic inpatients with schizophrenia: a randomized double-blind study. Int Clin Psychopharmacol. 2001;16(6):325-30. PMID:11712620

151. Lim HK, Kim JJ, Pae CU, et al. Comparison of risperidone orodispersible tablet and intramuscular haloperidol in the treatment of acute psychotic agitation: a randomized open, prospective study. Neuropsychobiology. 2010;62(2):81-6. PMID:20523078

152. Chiu E, Burrows G, Stevenson J. Double-blind comparison of clozapine with chlorpromazine in acute schizophrenic illness. Aust NZ J Psychiatry. 1976;10(4):343-7. PMID:798582

153. Ekblom B, Haggstrom JE. Clozapine (Leponex) compared with chlorpromazine: a double-blind evaluation of pharmacological and clinical properties. Curr Ther Res Clin Exp. 1974;16(9):945-57. PMID:4154183

154. Gelenberg AJ, Doller JC. Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double-blind study. J Clin Psychiatry. 1979;40(5):238-40. PMID:374401

155. Itoh H, Miura S, Yagi G, et al. Some methodological considerations for the clinical evaluation of neuroleptics: comparative effects of clozapine and haloperidol on schizophrenics. Folia Psychiatr Neurol Jpn. 1977;31(1):17-24. PMID:863344

156. Leon CA. Therapeutic effects of clozapine: a 4-year follow-up of a controlled clinical trial. Acta Psychiatr Scand. 1979;59(5):471-80. PMID:380268

157. Rinieris P, Christodoulou GN, Souvatzoglou A, et al. Free-thyroxine index in schizophrenic patients before and after neuroleptic treatment. Neuropsychobiology. 1980;6(1):29-33. PMID:6102744

158. Shopsin B, Klein H, Aaronsom M, et al. Clozapine, chlorpromazine, and placebo in newly hospitalized, acutely schizophrenic patients: a controlled, double-blind comparison. Archives of General Psychiatry. 1979;36(6):657-64. PMID:375865

159. Avasthi A. Olanzapine in the treatment of schizophrenia: an open label comparitive trial from North India. Indian J Pscychiatry. 2001;43(3):257-63. PMID:21407865

160. Guirguis E, Voineskos G, Gray J. Clozapine (Leponex) vs chlorpromazine (Largatil) in acute schizophrenia: a double-blind controlled study. Curr Ther Res Clin Exp. 1977;21:707-19.

161. Singer K, Law SK. A double-blind comparison of clozapine (Leponex) and chlorpromazine in schizophrenia of acute symptomatology. J Int Med Res. 1974;2:433-5.

162. Gaszner P, Makkos Z. Clozapine maintenance therapy in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(3):465-9. PMID:15093952

163. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ. 2002;325(7372):1070. PMID:12424166

164. Als-Nielsen B, Gluud LL, Gluud C. Methodological quality and treatment effects in randomised trials: a review of six empirical studies. 112th Cochrane Colloquium Oct 2-6, Ottawa, Ontario, Canada 2004.

165. Pildal J, Hrobjartsson A, Jorgensen KJ, et al. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol. 2007;36(4):847-57. PMID:17517809

166. Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. Contemp Clin Trials. 2008;29(2):109-13. PMID:17919992

167. Clark SL, Adkins DE, van den Oord EJ. Analysis of efficacy and side effects in CATIE demonstrates drug response subgroups and potential for personalized medicine. Schizophr Res. 2011;132(2-3):114-20. PMID:121872442

168. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951;41(3):279-281.

Abbreviations

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDS–S	Calgary Depression Scale for Schizophrenia
CER	Comparative effectiveness review
CGI–BP	Clinical Global Impression–Bipolar
CGI–I	Clinical Global Impression–Improvement
CGI–S	Clinical Global Impression–Severity
CI	Confidence interval
CNS	Central nervous system
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
ECG	Electrocardiogram
EPC	Evidence-based Practice Center
EPS	Extrapyramidal symptom or syndrome
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
I^2	I-squared
IQR	Interquartile range
KQ	Key question
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Mean difference
nRCTs	Nonrandomized controlled trial
PANSS	Positive and Negative Symptom Scale
RCT	Randomized controlled trial
SAE	Serious adverse event
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCL	Symptom Checklist
SoE	Strength of evidence
SGA	Second-generation antipsychotic
YMRS	Young Mania Rating Scale

Appendix A. Literature Search Strategies

Table A–1. MEDLINE®–Ovid Version

Date searched: 15Jul10 (reviews); 22Jul10 (RCTs); 9Aug10 (cohort studies); 13April11 (all study designs); 11Jul11(all study designs)
Notes: limit to: RCT/CCT, cohort studies, systematic reviews, English only, 1950–present, adult (19–64 years)

1. exp Schizophrenia/
2. Schizophrenia, Catatonic/
3. Schizophrenia, Disorganized/
4. Schizophrenia, Paranoid/
5. Psychotic Disorders/
6. Schizotypal Personality Disorder/
7. schizophreniform.tw.
8. (schizoaffective or schizo-affective).tw.
9. schizophren$.mp.
10. (dementia adj (praecox or precox)).tw.
11. (delusional adj2 disorder*).tw.
12. ((negative or positive) adj syndrome*).tw.
13. hebephrenia.tw.
14. exp Bipolar Disorder/
15. (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress$)) or mania*).tw.
16. (BPD or hypoman$ or manic-depressive).tw.
17. (BP 1 or BP 2 or BP I or BP II).tw.
18. (cyclothym$ or euthymic).tw.
19. (acute adj2 mania).tw.
20. (acute adj2 mixed adj episode*).tw.
21. (rapid-cycling adj5 bipolar).tw.
22. (rapid adj2 cycling adj5 bipolar).tw.
23. (mixed adj2 state* adj3 bipolar).tw.
24. or/1-23
25. exp Antipsychotic Agents/
26. exp Tranquilizing Agents/
27. (neuroleptic adj2 (agent* or drug*)).tw.
28. or/25-27
29. ((first or 1st) adj generation adj antipsychotic*).tw.
30. chlorpromazine/
31. 50-53-3.rn.
32. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
63. methotrimeprazine/
64. 60-99-1.rn.
65. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
66. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
67. Butyrophenones/ad, to, tu, ct, po, ae
68. Thioxanthenes/ad, to, tu, ct, po, ae
69. Dibenzoxazepines/ad, to, tu, ct, po, ae
70. Indoles/ad, to, tu, ct, po, ae
71. or/29-70
72. atypical antipsychotic$.tw.
73. ((second or 2nd) adj generation adj antipsychotic*).tw.
74. ((third or 3rd) adj generation adj antipsychotic*).tw.
75. Asenapine/
76. 65576-45-6.rn.
77. (Asenapine or EINECS 265-829-4).mp.
78. clozapine/
79. 5786-21-0.rn.
80. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
81. risperidone/
82. 106266-06-2.rn.
83. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
84. olanzapine.mp.
85. 132539-06-1.rn.
86. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina

Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
33. Droperidol/
34. 548-73-2.rn.
35. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
36. fluphenazine/
37. 69-23-8.rn.
38. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
39. haloperidol/
40. 52-86-8.rn.
41. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
42. loxapine/
43. 1977-10-2.rn.
44. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
45. perphenazine/
46. 58-39-9.rn.
47. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
48. Pimozide/
49. 2062-78-4.rn.
50. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
51. Prochlorperazine/
52. 58-38-8.rn.
53. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
54. thiothixene/
55. 5591-45-7.rn.
or Olanzapinum or Olansek or Zalasta or Zypadhera or Symbyax).mp.
87. quetiapine.mp.
88. (111974-69-7 or 111974-72-2).rn.
89. (Co-Quetiapine or HSDB 7557 or Seroquel).mp.
90. ziprasidone.mp.
91. 146939-27-7.rn.
92. (Zeldox or zeldrox or geodon).mp.
93. aripiprazole.mp.
94. 129722-12-9.rn.
95. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
96. paliperidone.mp.
97. 144598-75-4.rn.
98. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
99. Iloperidone/
100. 133454-47-4.rn.
101. (Fanapt or Iloperidone or HP 873 or Zomaril).mp.
102. Isoxazoles/ad, to, tu, ct, po, ae
103. Dibenzazepines/ad, to, tu, ct, po, ae
104. Pyrimidinones/ad, to, tu, ct, po, ae
105. Piperidines/ad, to, tu, ct, po, ae
106. Dibenzothiazepines/ct, ad, to, tu, ae, po
107. Piperazines/ad, tu, to, ct, po, ae
108. Pirenzepine/tu, ad, to, ct, po, ae
109. Thiazoles/ad, th, ct, po, to, ae
110. Quinolones/to, po, ct, ad, tu, ae
111. or/72-110
112. and/71,111
113. and/28,71,111
114. or/112-113
115. randomized controlled trial.pt.
116. controlled clinical trial.pt.
117. randomi?ed.ab.
118. placebo*.ab.
119. drug therapy.fs.
120. randomly.ab.
121. trial.ab.
122. groups.ab.
123. or/115-122
124. humans/ not (animals and humans).hw,sh.
125. 123 and 124
126. and/24,114,125
127. limit 126 to yr="1987 - 2010"
128. limit 127 to english language
129. limit 126 to yr="1950 - 1986"
130. limit 129 to english language
131. cohort studies/
132. followup studies/
133. longitudinal studies/
134. prospective studies/
135. Retrospective Studies/
136. (observation$ or prospectiv$ or retrospectiv$ or cohort$ or control$ or volunteer$ or evaluat$ or compar$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial$).ti,ab,sh.
137. or/131-136
138. humans.hw,sh.
139. and/137-138
140. meta-analysis.mp,pt.

56. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.	141. review.pt. 142. search:.tw. 143. or/140-142
57. trifluoperazine/	144. and/24,114,139
58. 117-89-5.rn.	145. and/24,114,143
59. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.	146. limit 145 to yr="1987 - 2010" 147. limit 146 to english language 148. limit 145 to yr="1950 - 1986" 149. limit 148 to english language 150. limit 144 to yr="1987-2010" 151. limit 150 to english language 152. limit 144 to yr="1950-1986" 153. limit 152 to english language
60. thioridazine/	
61. 50-52-2.rn.	
62. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or	

CCT = controlled clinical trial; RCT = randomized controlled trial

Table A–2. PsycINFO–Ovid Version

Date searched: 16Jul10; 13April11; 11Jul11

Notes: limit to: RCT/CCT, cohort studies, systematic reviews, English only, 1950-–present

1. exp schizophrenia/
2. exp "fragmentation (schizophrenia)"/
3. exp "positive and negative symptoms"/
4. exp schizoaffective disorder/
5. exp schizoid personality disorder/
6. exp schizotypal personality disorder/
7. exp psychosis/
8. or/1-7
9. schizophren*.mp.
10. (schizoaffective or schizo-affective).tw.
11. (dementia adj praecox).tw.
12. (delusional adj2 disorder*).tw.
13. ((negative or positive) adj syndrome*).tw.
14. hebephrenia.tw.
15. or/9-14
16. or/8,15
17. exp Bipolar Disorder/
18. affective psychosis/
19. mania/
20. exp affective disorders/
21. or/17-20
22. (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress$)) or mania*).tw.
23. (BPD or hypoman$ or manic-depressive).tw.
24. (BP 1 or BP 2 or BP I or BP II).tw.
25. (cyclothym$ or euthymic).tw.
26. (acute adj2 mania).tw.
27. (acute adj2 mixed adj episode*).tw.
28. (rapid-cycling adj5 bipolar).tw.
29. (rapid adj2 cycling adj5 bipolar).tw.
30. (mixed adj2 state* adj3 bipolar).tw.
31. or/22-30
32. or/21,31
33. or/16,32
34. exp Neuroleptic Drugs/
35. ((first or 1st) adj generation adj antipsychotic*).tw.
36. exp Chlorpromazine/
37. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
38. Droperidol.mp.
39. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
40. exp Fluphenazine/
41. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
54. exp Thiothixene/
55. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene or Thiothixene).mp.
56. exp Trifluoperazine/
57. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus or Trifluperazine).mp.
58. or/35-57
59. ((second or 2nd) adj generation adj antipsychotic*).tw.
60. ((third or 3rd) adj generation adj antipsychotic*).tw.
61. exp Aripiprazole/
62. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
63. Asenapine.mp.
64. (Blonanserin or AD 5423).mp.
65. Iloperidone.mp.
66. (Fanapt or HP 873 or Zomaril).mp.
67. exp Olanzapine/
68. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Olanzapine or Zalasta or Zypadhera or Symbyax).mp.
69. paliperidone.tw.
70. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
71. exp Quetiapine/
72. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
73. exp Risperidone/
74. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
75. ziprasidone.tw.
76. (Zeldox or zeldrox or geodon).mp.
77. or/59-76
78. or/34,58,77
79. or/58,77
80. or/78-79
81. randomi?ed controlled trial.tw,pt.
82. exp Clinical Trials/
83. controlled clinical trial.tw,pt.
84. randomi?ed.ab.
85. placebo*.ab.
86. randomly.ab.
87. trial.ab.
88. groups.ab.
89. or/81-88
90. exp Animals/
91. 89 not 90
92. and/33,80,91
93. limit 92 to english language
94. limit 93 to (adulthood <18+ years> and "300

Siqualon or Triflumethazine or Valamina or Vespazine).mp. 42. exp Haloperidol/ 43. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp. 44. exp Loxapine/ 45. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM Sinophenin or Talofen or Talofen or Tomil or Verophen).mp. 46. exp Perphenazine/ 47. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp. 48. Pimozide/ 49. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp. 50. Prochlorperazine/ 51. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp. 52. exp Thioridazine/ 53. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or	adulthood ") 95. exp Clinical Trials/ 96. clinical trial:.mp. 97. random:.tw. 98. placebo:.mp. 99. double-blind:.mp. 100. or/95-99 101. and/33,80,100 102. limit 101 to english language 103. limit 102 to yr="1950 - 1986" 104. limit 102 to (adulthood <18+ years> and "300 adulthood ") 105. limit 104 to "0100 journal" 106. exp Followup Studies/ 107. exp longitudinal studies/ 108. exp prospective studies/ 109. exp retrospective studies/ 110. (observation$ or prospectiv$ or cohort$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial$).ti,ab,sh. 111. or/106-110 112. exp Animals/ 113. 111 not 112 114. and/33,80,113 115. limit 114 to english language 116. limit 115 to yr="1950 - 1986" 117. limit 115 to "0100 journal" 118. meta-analys?s.mp. 119. search:.tw. 120. review:.mp. 121. or/118-120 122. and/33,80,121 123. and/33,80 124. limit 123 to "0830 systematic review" 125. or/122,124 126. limit 125 to english language 127. limit 126 to (adulthood <18+ years> and "300 adulthood ") 128. limit 127 to "0100 journal" 129. adult*.mp. 130. 125 and 129 131. limit 130 to "0100 journal" 132. 128 or 131 133. limit 132 to yr="1950 - 1986"

CCT = controlled clinical trial; RCT = randomized controlled trial

Table A–3. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects–Wiley Version, International Pharmaceutical Abstracts (IPAB)

Date searched: 19Jul10; 4Oct10; 13April11; 11Jul11
Notes: text word searching for CDSR, CENTRAL, IPA

1. schizophren$.mp.
2. (schizoaffective or schizo-affective).tw.
3. (delusional adj2 disorder*).tw.
4. ((negative or positive) adj syndrome*).tw.
5. hebephrenia.tw.
6. Schizo$.mp.
7. or/1-6
8. bipolar$.mp.
9. (manic or mania).mp.
10. (acute adj2 mixed adj episode*).tw.
11. (BP 1 or BP 2 or BP I or BP II).tw.
12. (BPD or hypoman$ or manic-depressive).tw.
13. or/8-12
14. 7 or 13
15. (antipsychotic adj2 (drug* or agent*)).mp.
16. (neuroleptic adj2 (drug* or agent*)).mp.
17. or/15-16
18. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
19. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
20. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
21. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
22. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM Sinophenin or
26. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
27. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene or Thiothixene).mp.
28. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus or Trifluperazine).mp.
29. ((first or 1st) adj2 generation adj2 antipsychotic*).tw.
30. or/18-29
31. ((second or 2nd) adj generation adj antipsychotic*).tw.
32. ((third or 3rd) adj generation adj antipsychotic*).tw.
33. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
34. (Asenapine or Blonanserin or AD 5423).mp.
35. (Fanapt or HP 873 or Iloperidone or Zomaril).mp.
36. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Olanzapine or Zalasta or Zypadhera or Symbyax).mp.
37. (9-Hydroxyrisperidone or Invega or Paliperidone or R 76477 or RO76477).mp.
38. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
39. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
40. (Zeldox or zeldrox or Ziprasidone or geodon).mp.
41. or/31-40
42. and/14,30,41
43. and/14,17,30,41
44. or/42-43
45. adult*.mp.
46. 44 and 45
47. (pediatric or child* or youth or teen* or adolescen* or elderly or aged).mp.
48. 44 not 47
49. or/46,48
50. randomi?ed.mp.
51. trial*.tw.
52. random:.tw.
53. or/50-52
54. and/49,53

Talofen or Talofen or Tomil or Verophen).mp.
23. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
24. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
25. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
55. and/44,53
56. (cohort$ or longitudinal or retrospective or prospective or followup or case-control).mp.
57. and/49,56
58. limit 57 to yr="1987 -current"
59. limit 57 to yr="1950 -1986"
60. review:.mp.
61. search:.tw.
62. meta-analys?s:.mp.
63. or/60-62
64. and/49,63
65. and/44,63
66. limit 55 to (english language and yr="1987 - Current") [Limit not valid in CCTR,CDSR; records were retained]
67. limit 55 to yr="1950 -1986"
68. limit 44 to (english language and yr="1987 - current") [Limit not valid in CCTR,CDSR; records were retained]
69. limit 44 to yr="1950 -1986"

CDSR = Cochrane Database of Systematic Reviews; IPA = International Pharmaceutical Abstracts

Table A–4. CINAHL® (Cumulative Index to Nursing & Allied Health Literature)–EBSCO Version

Date searched: 21Jul10; 13April11; 11Jul11

S1 (MH "Schizophrenia+")
S2 (MH "Schizotypal Personality Disorder")
S3 schizophren* or schizotypal or (schizoaffective or schizo-affective) or (dementia praecox OR dementia precox) or negative syndrome or positive syndrome or hebephrenia
S4 (MH "Bipolar Disorder+")
S5 bipolar illness* or bipolar disorder* or bipolar psychos* or bipolar depress* or (BPD OR BP1 or BP2 or BP I or BP II)
S6 manic illness* or manic disorder* or manic psychos* or (manic depress* or manic-depress*) or hypoman*
S7 cyclothym* or euthymic or rapid-cycling or mixed state
S8 S1 or S2 or S3 or S4 or S5 or S6 or
S9 (MH "Antipsychotic Agents+")
S10 first generation antipsychotic* or 1st generation antipsychotic
S11 MH chlorpromazine or TX chlorpromazine
S12 ("droperidol") or (MH "Droperidol")
S13 ("fluphenazine") or (MH "Fluphenazine")
S14 ("haloperidol") or (MH "Haloperidol")
S15 loxapine
S16 perphenazine
S17 pimozide
S18 ("prochlorperazine") or (MH "Prochlorperazine")
S19 Thiothixene
S20 trifluperazine
S21 ("trifluoperazine") or (MH "Trifluoperazine Hydrochloride")
S22 ("Thioridazine") or (MH "Thioridazine
S23 methotrimeprazine
S24 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S25 second generation antipsychotic* or 2nd generation antipsychotic*
S26 asenapine
S27 ("clozapine") or (MH "Clozapine
S28 ("risperidone") or (MH "Risperidone")
S29 ("olanzapine") or (MH "Olanzapine")
S30 ("quetiapine") or (MH "Quetiapine")
S31 ziprasidone
S32 ("Aripiprazole") or (MH "Aripiprazole")
S33 paliperidone
S34 iloperidone
S35 S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34
S36 randomi$ed or random* or TX trial*
S37 (MH "Clinical Trials+")
S38 S36 or S37
S40 S8 and S24 and S35 and S38 Limiters - Human; Language: English; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years
S39 S8 and S24 and S35 and S38

Table A–5. SCOPUS

Date searched: 1987–Present (22Jul10); 1950–1986 (04Oct10); 13April11; 11Jul11

1987–Present

(((((TITLE-ABS-KEY((schizophren* OR schizotypal OR schizoaffective OR schizo-affective OR hebephrenia) OR (dementia PRE/1 pr?ecox) OR (bipolar W/2 disorder*) OR (bipolar W/2 illness*) OR (bipolar W/2 psychos?s) OR (bipolar W/2 depress*) OR (bpd OR bp1 OR bp2 OR bp i OR bp ii) OR (hypoman* OR manic-depress OR cyclothym* OR euthymic OR rapid-cycling))) AND (KEY(antipsychotic* OR neuroleptic*)) AND ((TITLE-ABS-KEY((first PRE/1 generation PRE/1 antipsychotic*) OR (1st PRE/1 generation PRE/1 antipsychotic) OR (first PRE/1 generation PRE/1 neuroleptic*) OR (1st PRE/1 generation PRE/1 neuroleptic*) OR (typical PRE/1 antipsychotic*) OR (typical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((chlorpromazine) OR (droperidol) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (perphenazine) OR (pimozide) OR (prochlorperazine) OR (thiothixene OR tiotixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine)))) AND ((TITLE-ABS-KEY((second PRE/1 generation PRE/1 antipsychotic*) OR (2nd PRE/1 generation PRE/1 antipsychotic) OR (second PRE/1 generation PRE/1 neuroleptic*) OR (2nd PRE/1 generation PRE/1 neuroleptic*) OR (atypical PRE/1 antipsychotic*) OR (atypical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((asenapine) OR (clozapine) OR (risperidone) OR (olanzapine OR symbyax) OR (quetiapine) OR (ziprasidone OR zeldox OR geodon) OR (aripiprazole) OR (paliperidone) OR (iloperidone))))) AND (LANGUAGE(english)) AND (PUBYEAR AFT 1986)) AND (SRCTYPE(j))) AND (TITLE-ABS-KEY((rct OR random* OR trial*) OR (control* PRE/2 trial*) OR (clinical PRE/2 trial*)))) AND (DOCTYPE(ar)) AND (KEY(human))

1950–1986

((((((TITLE-ABS-KEY((schizophren* OR schizotypal OR schizoaffective OR schizo-affective OR hebephrenia) OR (dementia PRE/1 pr?ecox) OR (bipolar W/2 disorder*) OR (bipolar W/2 illness*) OR (bipolar W/2 psychos?s) OR (bipolar W/2 depress*) OR (bpd OR bp1 OR bp2 OR bp i OR bp ii) OR (hypoman* OR manic-depress OR cyclothym* OR euthymic OR rapid-cycling))) AND (KEY(antipsychotic* OR neuroleptic*)) AND ((TITLE-ABS-KEY((first PRE/1 generation PRE/1 antipsychotic*) OR (1st PRE/1 generation PRE/1 antipsychotic) OR (first PRE/1 generation PRE/1 neuroleptic*) OR (1st PRE/1 generation PRE/1 neuroleptic*) OR (typical PRE/1 antipsychotic*) OR (typical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((chlorpromazine) OR (droperidol) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (perphenazine) OR (pimozide) OR (prochlorperazine) OR (thiothixene OR tiotixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine)))) AND ((TITLE-ABS-KEY((second PRE/1 generation PRE/1 antipsychotic*) OR (2nd PRE/1 generation PRE/1 antipsychotic) OR (second PRE/1 generation PRE/1 neuroleptic*) OR (2nd PRE/1 generation PRE/1 neuroleptic*) OR (atypical PRE/1 antipsychotic*) OR (atypical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((asenapine) OR (clozapine) OR (risperidone) OR (olanzapine OR symbyax) OR (quetiapine) OR (ziprasidone OR zeldox OR geodon) OR (aripiprazole) OR (paliperidone) OR (iloperidone))))) AND (LANGUAGE(english)) AND (PUBYEAR BEF 1986)) AND (SRCTYPE(j))) AND (TITLE-ABS-KEY((rct OR random* OR trial*) OR (control* PRE/2 trial*) OR (clinical PRE/2 trial*)))) AND (DOCTYPE(ar)) AND (KEY(human))) AND NOT (KEY(animal*))

Appendix B. Sample Data Extraction and Quality Assessment Forms

Comparative Effectiveness of FGA and SGA

RefID: **Reviewer's name:**

Inclusion/ Exclusion:

(1) **Is this a full-text manuscript published in English (e.i. not a conference proceeding, letter to the editor nor a foreign language publication) ?**

(2) Is the study population same as our inclusion criteria?
If no, then please state the reason for exclusion (e.g., age, schizophrenia, bipolar disorder):

(3) Is there an intervention/ comparator of interest to this review?

(4) What was the study design?

(5) What is the study population?

☐	*Schizophrenia*	☐	*Bipolar disorder*

(6) What was the intervention?

☐	*Chlorpromazine*	☐	*Pimozide*
☐	*Droperidol*	☐	*Prochlorperazine*
☐	*Fluphenazine*	☐	*Thioridazine*
☐	*Haloperidol*	☐	*Thiothixene*
☐	*Loxapine*	☐	*Trifluoperazine*
☐	*Perphenazine*		*Other... please describe:*

(7) What was the control?

☐	*Aripiprazole*	☐	*Paliperidone*
☐	*Asenapine*	☐	*Quetiapine*
☐	*Clozapine*	☐	*Risperidone*
☐	*Iloperidone*	☐	*Ziprasidone*
☐	*Olanzapine ± Fluoxetine*		*Other... please describe:*

Reviewer's Decision:

Reviewer's Comments:

1

First versus Second Generation Antipsychotics (Adults)

Refid: **Study Name:** **Reviewer's name:**

Study Demographics:

Study design		***Registration # (if available)***	
Country		***Number of centers (n)***	( )
Setting		***Funding (If pharm., company name)***	( )
Diagnosis		***DSM classification***	If other, please state:
Race		***Co-morbidities (e.g. DM)***	
Disease history:	Occurrence: Resistance:	***History of prior antipsychotic exposure***	Naivety: Drug:
Main inclusion criteria		***Main exclusion criteria***	
Use of concurrent standard medical therapies (e.g. Insulin)		***Study period (month and year)***	to
Washout period	Check if Washout period was used. ☐ Duration:	***Run-in phase***	Check if Run-in phase was used. ☐ Drug used: Duration:
Follow-up period			

Reviewer's Comments:

1

Medication characteristics:

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
Classification								
Drug								
Route of administration								
Dosage								
Dosage Intervals								
Other medications								

Reviewer's Comments:

Patient flow through trial:

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
Number screened								
Number randomized								
Number completed								
Number analyzed (efficacy)								
Number analyzed (safety)								

Reviewer's Comments:

Patient Baseline Demographics:

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
Age (yr) (random.) Mean ± SD	±	±	±	±	±	±	±	±
Body weight (Kg) Mean ± SD	±	±	±	±	±	±	±	±

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
Height (cm) *Mean ± SD*	±	±	±	±	±	±	±	±
BMI (Kg/ m²) *Mean ± SD*	±	±	±	±	±	±	±	±
Gender *Males*	/ %	/ %	/ %	/ %	/ %	/ %	/ %	/ %
Ethnicity *Caucasians*	/ %	/ %	/ %	/ %	/ %	/ %	/ %	/ %
Education (yrs) *Mean ± SD*	±	±	±	±	±	±	±	±

Reviewer's Comments:

Disease characteristics:

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
Age (yr) (diagnosis) *Mean ± SD*	±	±	±	±	±	±	±	±
Treatment (yr) *Mean ± SD*	±	±	±	±	±	±	±	±
Previous hospital admissions *Mean ± SD*	±	±	±	±	±	±	±	±

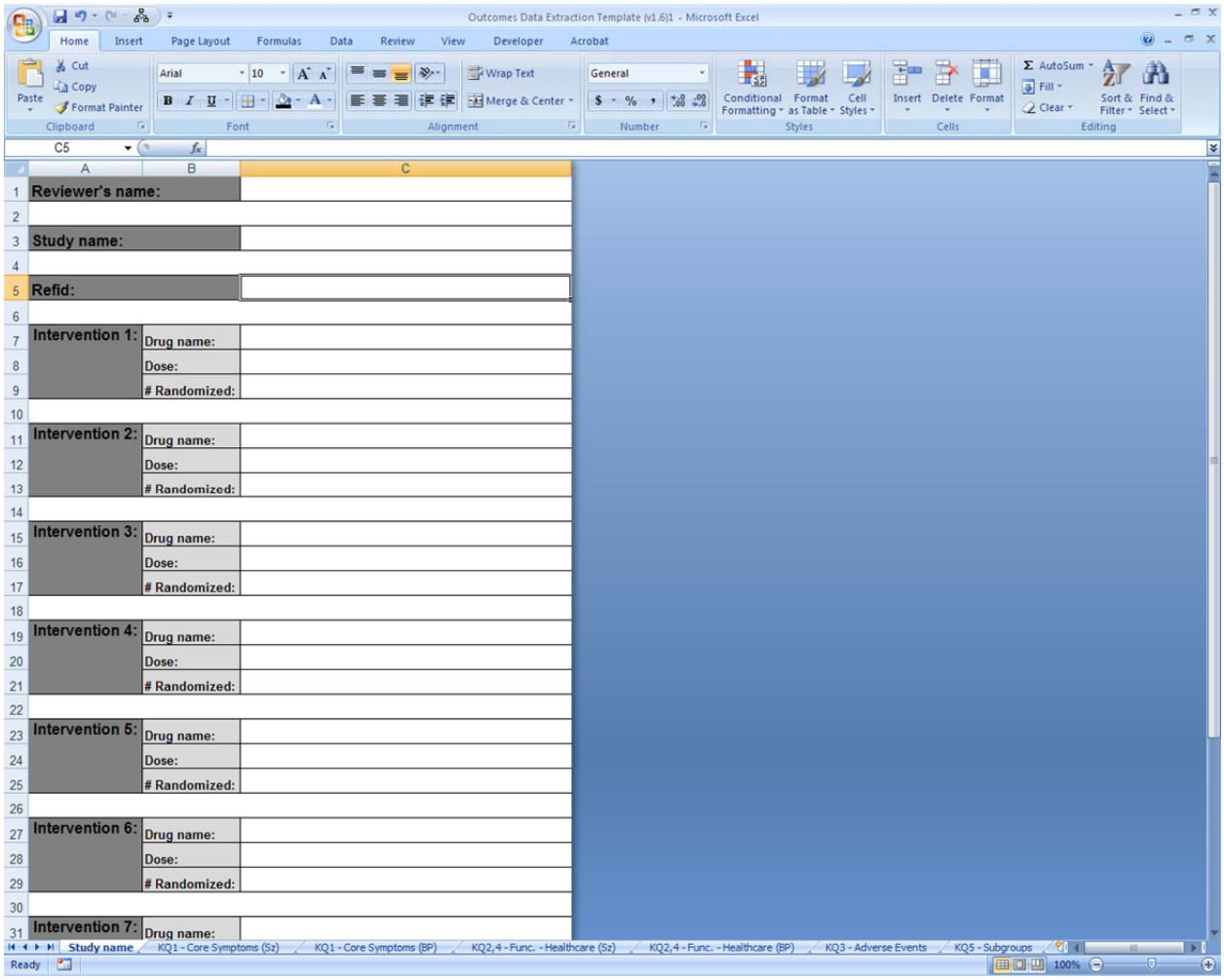
Reviewer's Comments:

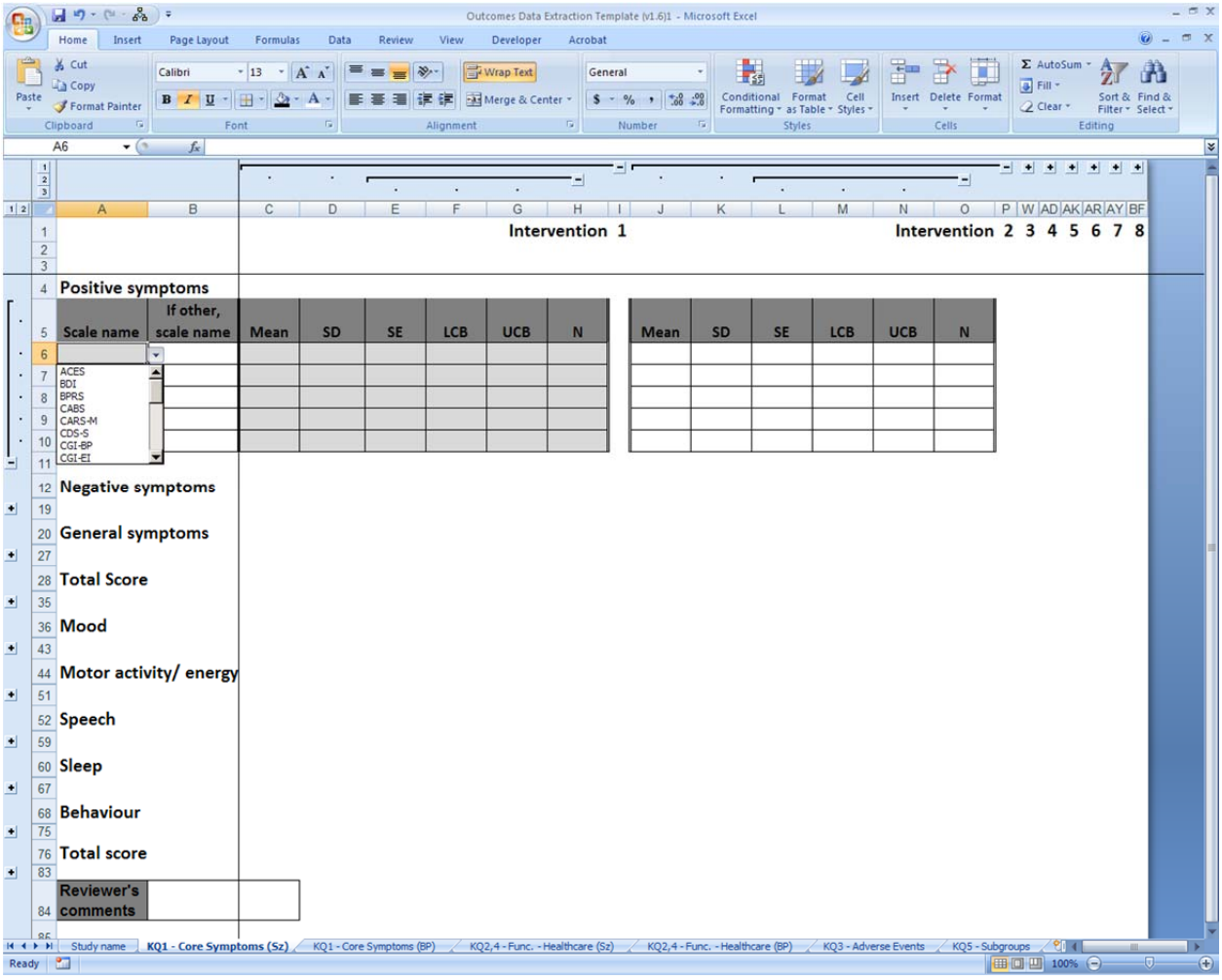
Baseline severity:

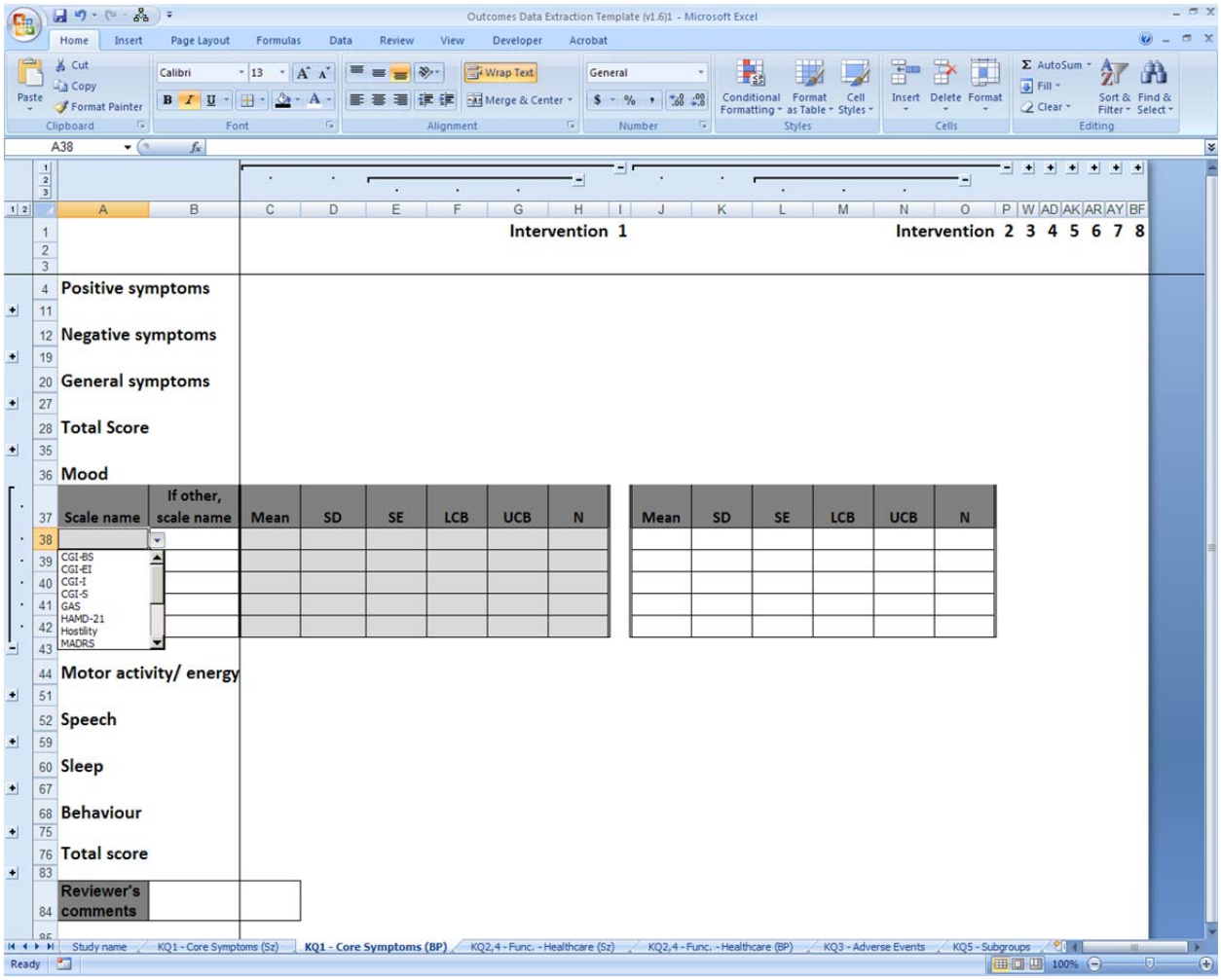
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
PANSS	±	±	±	±	±	±	±	±
BPRS	±	±	±	±	±	±	±	±
CGI-BP	±	±	±	±	±	±	±	±
CGI-EI	±	±	±	±	±	±	±	±
CGI-I	±	±	±	±	±	±	±	±
CGI-S	±	±	±	±	±	±	±	±
YMRS	±	±	±	±	±	±	±	±
GAS	±	±	±	±	±	±	±	±
MADRS	±	±	±	±	±	±	±	±

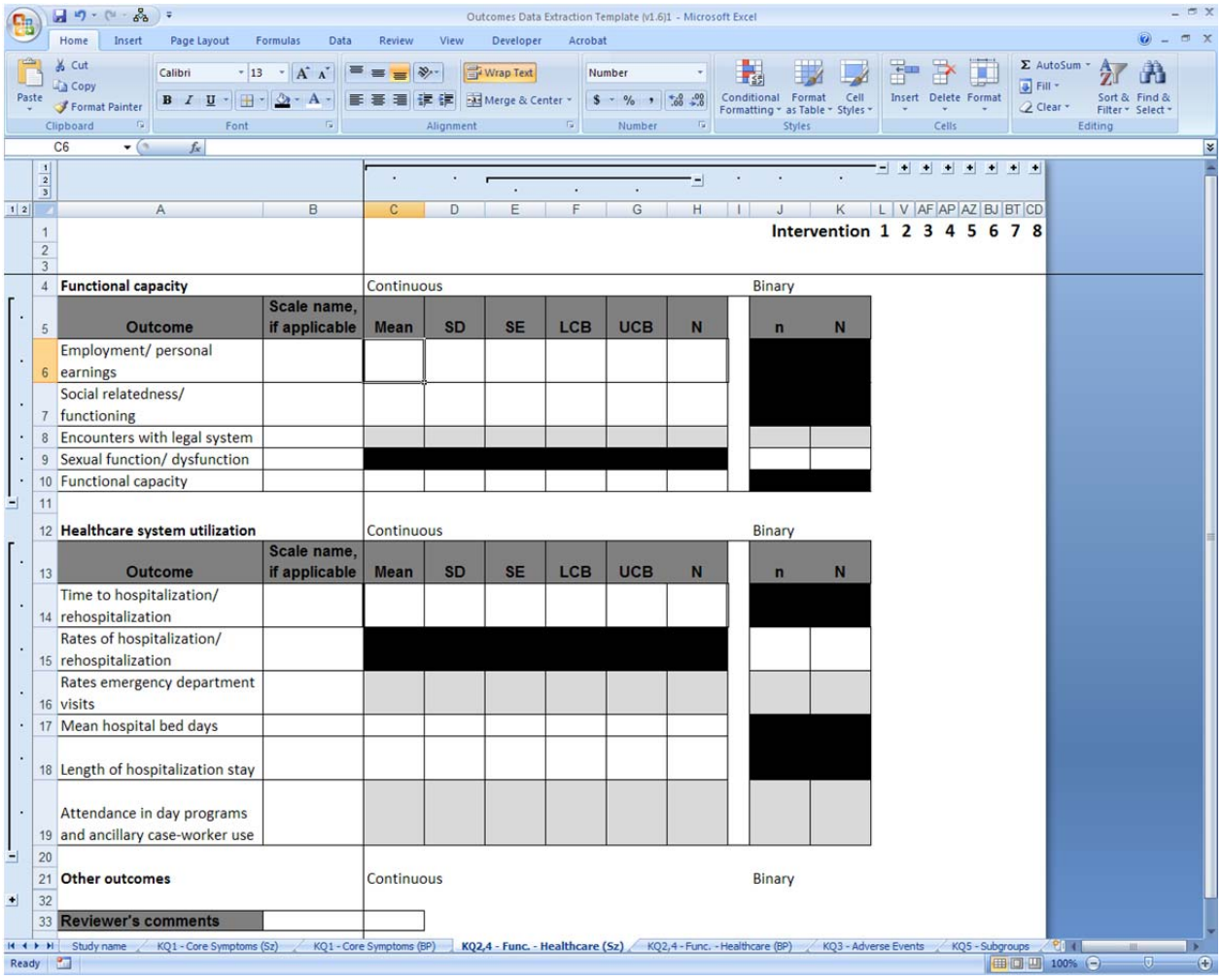
Reviewer's Comments:

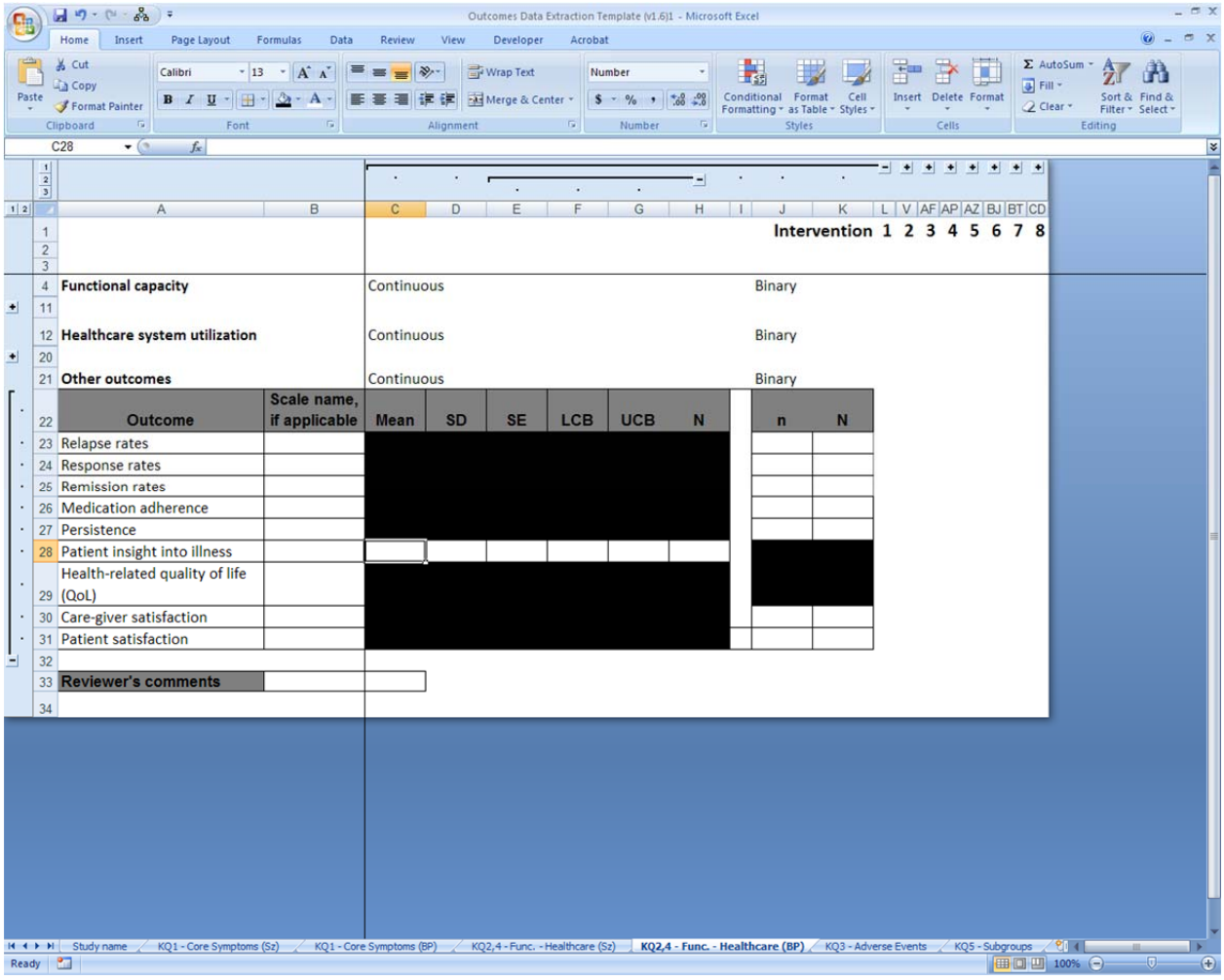
Reviewer's Overall Comments: Overall comments

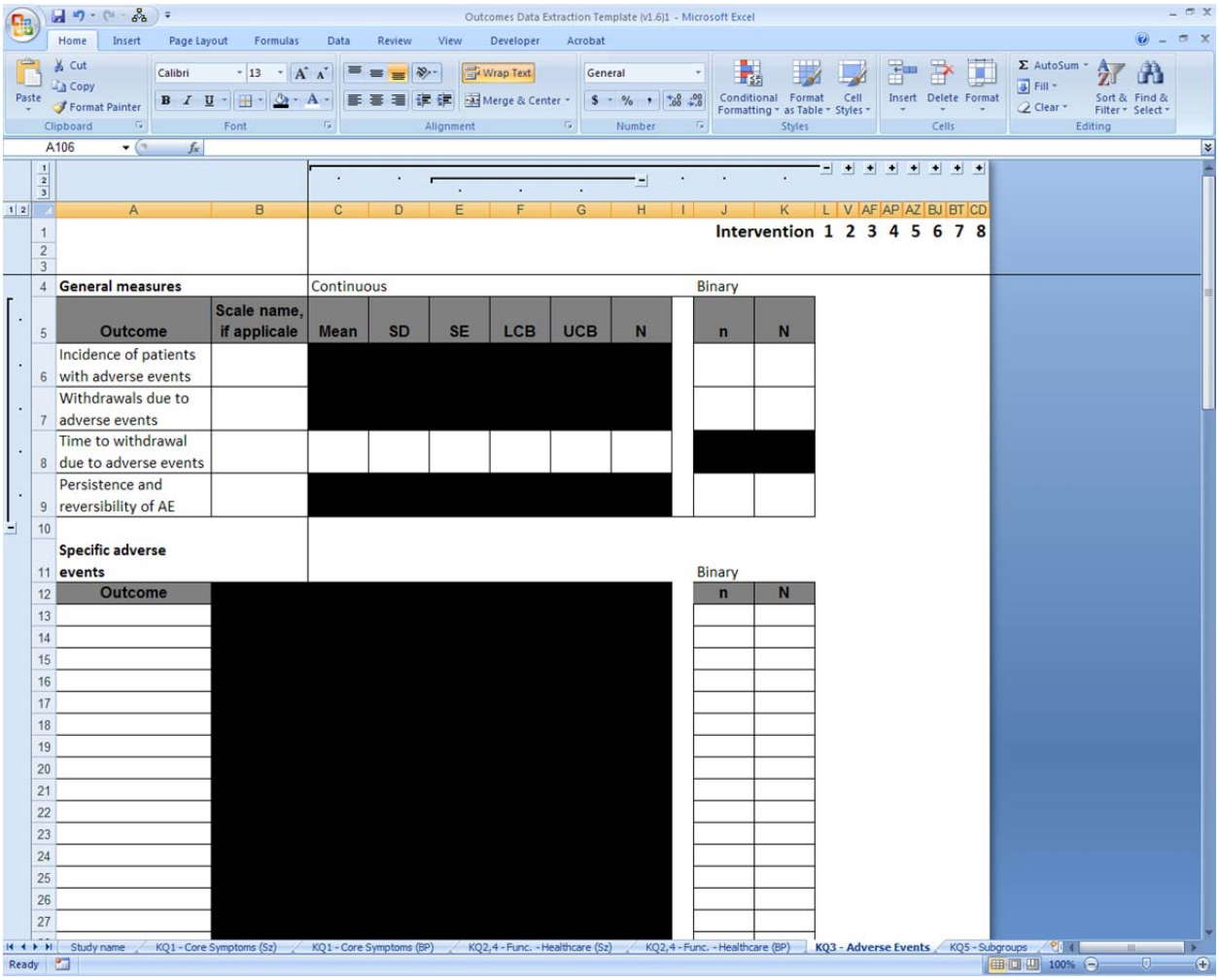

Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Home
Insert
Page Layout
Formulas
Data
Review
View
Developer
Acrobat
Reviewer's name:
Study name:
Refid:
Intervention 1:
Drug name:
Dose:
Randomized:
Intervention 2:
Intervention 3:
Intervention 4:
Intervention 5:
Intervention 6:
Intervention 7:
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready

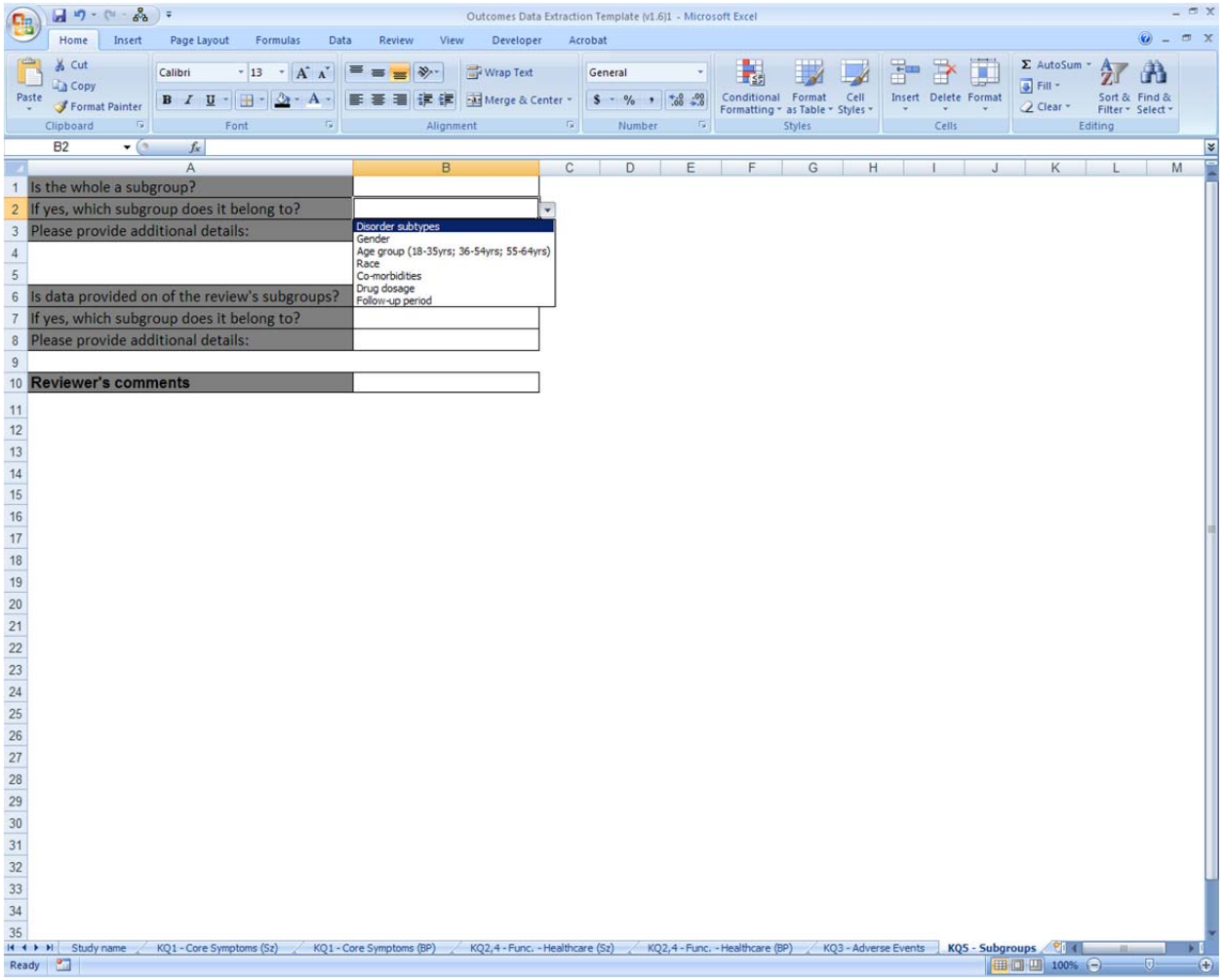

Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Intervention 1
Intervention 2
Positive symptoms
Scale name
If other, scale name
Mean
SD
SE
LCB
UCB
N
ACES
BDI
BPRS
CABS
CARS-M
CDS-S
CGI-BP
CGI-EI
Negative symptoms
General symptoms
Total Score
Mood
Motor activity/ energy
Speech
Sleep
Behaviour
Total score
Reviewer's comments
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready


Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Intervention 1
Intervention 2 3 4 5 6 7 8
Positive symptoms
Negative symptoms
General symptoms
Total Score
Mood
Scale name
If other, scale name
Mean
SD
SE
LCB
UCB
N
CGI-BS
CGI-EI
CGI-I
CGI-S
GAS
HAMD-21
Hostility
MADRS
Motor activity/ energy
Speech
Sleep
Behaviour
Total score
Reviewer's comments
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready


Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Intervention 1 2 3 4 5 6 7 8
Functional capacity
Continuous
Binary
Outcome
Scale name, if applicable
Mean
SD
SE
LCB
UCB
N
n
N
Employment/ personal earnings
Social relatedness/ functioning
Encounters with legal system
Sexual function/ dysfunction
Functional capacity
Healthcare system utilization
Continuous
Binary
Outcome
Scale name, if applicable
Mean
SD
SE
LCB
UCB
N
n
N
Time to hospitalization/ rehospitalization
Rates of hospitalization/ rehospitalization
Rates emergency department visits
Mean hospital bed days
Length of hospitalization stay
Attendance in day programs and ancillary case-worker use
Other outcomes
Continuous
Binary
Reviewer's comments
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready
100%


Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Intervention 1 2 3 4 5 6 7 8
Functional capacity
Continuous
Binary
Healthcare system utilization
Continuous
Binary
Other outcomes
Continuous
Binary
Outcome
Scale name, if applicable
Mean
SD
SE
LCB
UCB
N
n
N
Relapse rates
Response rates
Remission rates
Medication adherence
Persistence
Patient insight into illness
Health-related quality of life (QoL)
Care-giver satisfaction
Patient satisfaction
Reviewer's comments
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready


Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Intervention 1 2 3 4 5 6 7 8
General measures
Continuous
Binary
Outcome
Scale name, if applicale
Mean
SD
SE
LCB
UCB
N
n
N
Incidence of patients with adverse events
Withdrawals due to adverse events
Time to withdrawal due to adverse events
Persistence and reversibility of AE
Specific adverse events
Binary
Outcome
n
N
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready


Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel
Home
Insert
Page Layout
Formulas
Data
Review
View
Developer
Acrobat
Paste
Cut
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Clipboard
Calibri
13
Font
Wrap Text
Merge & Center
Alignment
General
Number
Conditional Formatting
Format as Table
Cell Styles
Styles
Insert
Delete
Format
Cells
AutoSum
Fill
Clear
Sort & Filter
Find & Select
Editing
B2
Is the whole a subgroup?
If yes, which subgroup does it belong to?
Please provide additional details:
Is data provided on of the review's subgroups?
If yes, which subgroup does it belong to?
Please provide additional details:
Reviewer's comments
Disorder subtypes
Gender
Age group (18-35yrs; 36-54yrs; 55-64yrs)
Race
Co-morbidities
Drug dosage
Follow-up period
Study name
KQ1 - Core Symptoms (Sz)
KQ1 - Core Symptoms (BP)
KQ2,4 - Func. - Healthcare (Sz)
KQ2,4 - Func. - Healthcare (BP)
KQ3 - Adverse Events
KQ5 - Subgroups
Ready
100%

RISK OF BIAS (ROB)
RANDOMIZED CONTROLLED TRIALS

Item	*Judgment*	*Description*
Adequate sequence generation?		
Allocation concealment?		
Blinding?		
Incomplete outcome data addressed?		
Free of selective reporting?		
Free of other bias?		

Appendix C. List of Excluded Studies

A total of 921 studies were excluded from the review during phase 2 screening. Reasons for exclusion included: a) publication type or study design (n = 612), b) non-English language (n = 100), c) population or intervention not of interest (n = 134), d) no extractable data related to the outcome of interest (n = 58), and e) publication unavailable through library service (n = 17).

Publication Type and Study Design

1. Abdollahian EM. Comparing the effects of risperidone and haloperidol in chronic schizophrenic patients. Proceedings of the Thematic Conference of the World Psychiatric Association on "Treatments in Psychiatry: An Update"; 2004.
2. Addington J, Addington D. Neurocognitive functioning in schizophrenia: a trial of risperidone versus haloperidol. Can J Psychiatry 1997;42(9):983. PMID:9429073
3. Addington J. Cognitive functioning in schizophrenia: a trial of risperidone versus haloperidol. 27th Collegium Internationale Neuro-psychopharmacologicum 2006.
4. Adetunji B, Basil B, Mathews M, et al. Methodological issues in a study of long-term maintenance therapy with quetiapine versus haloperidol decanoate. J Clin Psychiatry 2006;67(3):497-8. PMID:16649843
5. Agelink MW, Malessa R, Kamcili E, et al. Cardiovascular autonomic reactivity in schizophrenics under neuroleptic treatment: a potential predictor of short-term outcome? Neuropsychobiology 1998;38(1):19-24. PMID:9701718
6. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Archives of General Psychiatry 2003;60(12):1228-35. PMID:14662555
7. Aleman A, Kahn RS. Effects of the atypical antipsychotic risperidone on hostility and aggression in schizophrenia: a meta-analysis of controlled trials. Eur Neuropsychopharmacol 2001;11(4):289-93. PMID:11532383
8. Allan ER, Sison CE, Alpert M, et al. The relationship between negative symptoms of schizophrenia and extrapyramidal side effects with haloperidol and olanzapine. Psychopharmacol Bull 1998;34(1):71-4. PMID:9564201
9. Allison DB, Loebel AD, Lombardo I, et al. Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: effect modification or regression to the mean? Psychiatry Res 2009;170(2-3):172-6. PMID:19897253
10. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156(11):1686-96. PMID:10553730
11. Alvarez-Jimenez M, Gonzalez-Blanch C, Crespo-Facorro B, et al. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs 2008;22(7):547-62. PMID:18547125
12. Amann BL, Pogarell O, Mergl R, et al. EEG abnormalities associated with antipsychotics: a comparison of quetiapine, olanzapine, haloperidol and healthy subjects. Hum Psychopharmacol 2003;18(8):641-6. PMID:14696024
13. Ames D, Wirshing WC, Baker RW, et al. Predictive value of eosinophilia for neutropenia during clozapine treatment. J Clin Psychiatry 1996;57(12):579-81. PMID:9010121
14. Ames D. Risperidone vs. haloperidol: relative liabilities for ocd and depression. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia 1996;18(2-3):129.
15. Ames D. Subjective response to risperidone and haloperidol: preliminary results conference proceeding. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia 1996;18(2-3):129.
16. Ames D. Treatment resistant schizophrenia: evaluation of risperidone vs. haloperidol. Biol Psychiatry 1997;72S-3S.
17. Ames D. Treatment-resistant schizophrenia: efficacy of risperidone versus haloperidol. 150th Annual Meeting of the American Psychiatric Association 2000.
18. Amin M, Shukla VS. Olanzapine vs haloperidol for treatment of schizophrenia. JAMA 2004;291(9):1065-6. PMID:14996767
19. Andersen SW, Tollefson GD, Sanger TM. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol [conference abstract]. Schizophr Res 1999;269.
20. Andrade C. A mood stabilizer with risperidone or haloperidol for mania. Am J Psychiatry 2004;161(11):2140. PMID:15514435
21. Anutosh S, Ali MW, Ingenito. Controlled study of aripiprazole and haloperidol in schizophrenia. Eur Psychiatry 2002;(Suppl 1):103s.
22. Arbaizar B, Gomez-Acebo I, Llorca J. Quality of reporting controlled clinical trials on treatment of the acute mania phase of bipolar disorder with new antipsychotic drugs. Pharmacopsychiatry 2008;41(6):240-1. PMID:19067261

23. Arranz B. Does the intracellular signalling system associated to the serotonergic 5-HT2A receptor activation predict clinical response to olanzapine in drug-free schizophrenic patients? Eur Neuropsychopharmacol 2002;(Suppl 3):S266.
24. Ascher-Svanum H, Nyhuis A, Tunis S, et al. Time to all cause discontinuation following randomization to open-label olanzapine, risperidone, or conventional antipsychotic treatment for schizophrenia. 158th Annual Meeting of the American Psychiatric Association 2005.
25. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Clinical, functional, and economic ramifications of early nonresponse to antipsychotics in the naturalistic treatment of schizophrenia. Schizophr Bull 2008;34(6):1163-71. PMID:18156640
26. AstraZeneca. A multicenter, double-blind, randomized, comparison of quetiapine (seroquelA) and chlorpromazine in the treatment of subjects with treatment-resistant schizophrenia. http://www.clinicalstudyresults.org/
27. AstraZeneca. A multicentre, double-blind, randomised trial to compare the effects of seroquel and chlorpromazine in patients with treatment resistant schizophrenia (5077IL/0054 TRESS). http://www.clinicalstudyresults.org/2000.
28. AstraZeneca. An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Seroquel (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania [5077IL/0104]. http://www.clinicalstudyresults.org/
29. AstraZeneca. An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Seroquel (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania [5077IL/0104]. http://www.clinicalstudyresults.org/
30. Atmaca M. The comparison of quetiapine and haloperidol effects on serum prolactine in patients with schizophrenia. Eur Neuropsychopharmacol 2001;11(3):S240.
31. Attari A, Amini M, Mansoori S, et al. Comparison of incidence of diabetes mellitus in schizophrenic patients treated with atypical or typical antipsychotics. Eur Arch Psychiatry Clin Neurosci 2009;S84.
32. Avissar S, Roitman G, Schreiber G. Differential effects of the antipsychotics haloperidol and clozapine on G protein measures in mononuclear leukocytes of patients with schizophrenia. Cell Mol Neurobiol 2001;21(6):799-811. PMID:12043849
33. Awad AG, Voruganti LN, Mackell JA, et al. Ziprasidone versus haloperidol in acute schizophrenia: subjective tolerability. 156th Annual Meeting of the American Psychiatric Association, San Francisco CA 2003.
34. Ayd FJ. Aripiprazole: recent evidence-based clinical data. Int Drug Ther Newsl 2003;38(5)
35. Baggaley M. Sexual dysfunction in schizophrenia: focus on recent evidence. Hum Psychopharmacol 2008;23(3):201-9. PMID:18338766
36. Bagnall A, Kleijnen J, Leitner M, et al. Ziprasidone for schizophrenia and severe mental illness [systematic review]. Cochrane Database Syst Rev 2010;2010(5) PMID:10796670
37. Baker RW, Julier BE, Stauffer VL. Manic-like symptoms in schizophrenic patients treated with olanzapine, haloperidol and placebo. Eur Neuropsychopharmacol 2001;11(Suppl 3):S278-S279.
38. Barak Y, Swartz M, Plopsky I. Assessing cardiovascular risks of olanzapine treatment: a 6-month study versus haloperidol in schizophrenia patients. Int Clin Psychopharmacol 2005;20(6):315-7. PMID:16192840
39. Barbui C. "Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial": comment. The American Journal of Psychiatry 1998;155(1):152-3.
40. Barbui C. Randomized evaluation of the effectiveness of clozapine and aripiprazole versus clozapine and haloperidol in the treatment of schizophrenia: an independent, pragmatic, multicentre, parallel-group, superiority trial. http://www.clinicaltrials.gov
41. Bartzokis G, Lu PH, Nuechterlein KH, et al. Differential effects of typical and atypical antipsychotics on brain myelination in schizophrenia. Schizophr Res 2007;93(1-3):13-22. PMID:17407804
42. Basil B, Mathews M, Adetunji B, et al. The CATIE study. Am J Psychiatry 2006;163(3):555. PMID:16513895
43. Basson B. Factors influencing weight change in patients with schizophrenia treated with olanzapine verus haloperidol or risperidone. J Psychopharmacol 2000;(3 Suppl):A60.
44. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry 2001;62(4):231-8. PMID:11379836
45. Basu A, Meltzer HY, Dukic V. Estimating transitions between symptom severity states over time in schizophrenia: a Bayesian meta-analytic approach. Stat Med 2006;25(17):2886-910. PMID:16220519
46. Battaglia J, Houston JP, Ahl J, et al. A post hoc analysis of transitioning to oral treatment with olanzapine or haloperidol after 24-hour intramuscular treatment in acutely agitated adult patients with schizophrenia. Clin Ther 2005;27(10):1612-8. PMID:16330297
47. Battaglia J, Lindborg SR, Alaka K, et al. Calming versus sedative effects of intramuscular olanzapine in agitated patients. Am J Emerg Med 2003;21(3):192-8. PMID:12811711
48. Bayar R. A multi-centered study evaluating the effects of haloperidol and olanzapine on depressive symptoms in schizophrenic patients. Eur Neuropsychopharmacol 2005;(Suppl 3):S474.
49. Beasley C. Olanzapine versus haloperidol: long-term results of the multi-center international trial. Eur Neuropsychopharmacol 1996;6(Suppl 3):59.

50. Beasley CM, Dellva MA, Tamura RN, et al. Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. Br J Psychiatry 1999;174:23-30. PMID:10211147
51. Beasley CM, Stauffer VL, Liu-Seifert H, et al. All-cause treatment discontinuation in schizophrenia during treatment with olanzapine relative to other antipsychotics: an integrated analysis. J Clin Psychopharmacol 2007;27(3):252-8. PMID:17502771
52. Beasley CM, Tollefson GD, Tran PV. Efficacy of olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry 1997;58(Suppl 10):7-12. PMID:9265910
53. Bech P, Peuskens JC, Marder SR, et al. Meta-analytic study of the benefits and risks of treating chronic schizophrenia with risperidone or conventional neuroleptics. Eur Psychiatry 1998;13(6):310-4. PMID:19698646
54. Bedard MA, Scherer H, Delorimier J, et al. Differential effects of D2- and D4-blocking neuroleptics on the procedural learning of schizophrenic patients. Can J Psychiatry 1996;41(7 Suppl1) PMID:8884048
55. Beitinger R, Lin J, Kissling W, et al. Comparative remission rates of schizophrenic patients using various remission criteria. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(7):1643-51. PMID:18616969
56. Berk M, Ng F, Wang WV, et al. Going up in smoke: tobacco smoking is associated with worse treatment outcomes in mania. J Affective Disord 2008;110(1-2):126-34. PMID:18280579
57. Bersani G, Gherardelli S, Clemente R, et al. Neurologic soft signs in schizophrenic patients treated with conventional and atypical antipsychotics. J Clin Psychopharmacol 2005;25(4):372-5. PMID:16012282
58. Bhana N, Foster RH, Olney R, et al. Olanzapine: an updated review of its use in the management of schizophrenia. Drugs 2001;61(1):111-61. PMID:11217867
59. Bhattacharjee J, El-Sayeh HG. Aripiprazole versus typical antipsychotic drugs for schizophrenia [systematic review]. Cochrane Database Syst Rev 2010. PMID:18646161
60. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2008. PMID:18646161
61. Birkett DP. Clozapine compared with haloperidol for refractory schizophrenia. New Engl J Med 1998;338(4):267-8. PMID:9441246
62. Blin O. Anxiolytic profiles of levomepromazine, haloperidol and risperidone in 62 schizophrenic patients. Clin Pharmacol Ther 1992;(2):189.
63. Blin O. Anxiolytic profiles of risperidone, haloperidol, and levomepromazine in schizophrenia: a factorial and regression analysis. Proceedings of the 9th World Congress of Psychiatry; 1993:12.
64. Blin O. Comparison of anxiolytic properties of levomepromazine, haloperidol and risperidone in schizophrenic patients. Biol Psychiatry 1991;29:388.
65. Blin O. Comparison of risperidone, haloperidol and levomepromazine in schizophrenia: a factorial analysis and discriminant function analysis. Clin Neuropharmacol 1992;(Suppl 1. Pt B):169B.
66. Bobes J, Garc AP, Rejas J, et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: the results of the EIRE study. J Sex Marital Ther 2003;29(2):125-47. PMID:12623765
67. Bobes J, Rejas J, Garcia-Garcia M, et al. Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. Schizophr Res 2003;62(1-2):77-88. PMID:12765747
68. Bonham C, Abbott C. Are second generation antipsychotics a distinct class? J Psychiatr Pract 2008;14(4):225-31. PMID:18664891
69. Borison R. Risperidone versus haloperidol in acute exacerbations of chronic schizophrenia. Proceedings of the 1st International Risperidone Investigators' Meeting; 1992;1992-10.
70. Borison RL, Arvanitist LA, Miller BG. A comparison of five fixed doses 'seroquel' (Ici 204,636) With haloperidol and placebo in patients with schizophrenia conference proceeding. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia 2000:132.
71. Bouchard RH, Demers MF, Merette. Classical neuroleptics (CNLP) vs risperdone (RIS) interim 12 months efficacy of a long-term, naturalistic study in schizophrenics. 11th CINP Congress, Glasgow, Scotland 1998.
72. Bourin M. Aripiprazole versus haloperidol for maintained treatment effect in acute mania. 156th Annual Meeting of the American Psychiatric Association, San Francisco, CA 2000.
73. Bourin M. Aripiprazole vs. haloperidol for maintained treatment effect in acute mania. 16th Congress of the European College of Neuropsychopharmacology 2003.
74. Bowden CL, Ketter TA, Sachs GS. Acute mania treatment. J Clin Psychiatry 2005;66(12):1598-601.
75. Brahm NC, Gutierres SL, Carnahan RM. Quetiapine for acute mania in bipolar disorder. Am J Health-Syst Pharm 2007;64(10):1045-53. PMID:17494904
76. Brambilla P, Barale F, Caverzasi E, et al. Clozapine-treated subjects with treatment-resistant schizophrenia: a systematic review of experimental and observational studies. Int Clin Psychopharmacol 2002;17(4):189-95. PMID:12131603
77. Brecher M. Prolactin levels and adverse events in patients treated with risperidone. Sixth World Congress of Biological Psychiatry, Nice, France 1997;173S.
78. Brecher MB, Lemmens P. Tolerability and cardiovascular safety of risperidone. 150th Annual Meeting of the American Psychiatric Association, San Diego, CA 1997.

79. Breier A. A double-blind dose response study comparing intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology;2000:14.
80. Breier A. A one-year double-blind comparison of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in patients with schizophrenia. Schizophr Res 2003;274-5.
81. Breier A. Comparative efficacy of olanzapne and haloperidol for patients with treatment resistant schizophrenia. Schizophr Res 1999;1-3:271.
82. Bridle C, Palmer S, Bagnall AM, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technol Assess 2001;8(19):iii-iiv.
83. Bristol-Myers S. A multicenter, randomized, double-blind study of flexible doses of aripiprazole versus perphenazine in the treatment of patients with treatment-resistant schizophrenia. http://www clinicalstudyresults org/
84. Bristol-Myers S. A multicenter, randomized, double-blind study of aripiprazole and haloperidol in the maintained response to treatment for an acute manic episode. http://www.clinicalstudyresults.org/
85. Bristol-Myers S. A randomized, double-blind comparison of the efficacy and safety of aripiprazole intramuscular formula, haloperidol, or placebo in the treatment of acutely agitated patients with a diagnosis of schizophrenia or schizoaffective disorder. http://www.clinicalstudyresults.org/
86. Brook S J. Ziprasidone vs haloperidol for IM/oral therapy of acute schizophrenia. Proceedings of the 11th Congress of the Association of European Psychiatrists 2002;(Suppl 1):100s.
87. Brook S K. The efficacy and tolerability of intramuscular (IM) ziprasidone versus IM haloperidol in patients with acute, non-organic psychosis. 151st American Psychiatric Association Meeting 1998.
88. Brook S K. The efficacy and tolerability of intramuscular (Im) Ziprasidone versus im haloperidol in patients with acute, nonorganic pyschosis conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe, New Mexico USA 1999;17-21(272):1999.
89. Brook S W. IM/oral ziprasidone versus haloperidol in recent-onset schizophrenia. Proceedings of the 3rd International Conference on Early Psychosis 2002;28.
90. Brook S W. Sequential IM/oral ziprasidone versus haloperidol in schizophrenia with anxiety. Schizophr Res 2003.
91. Brook S W. Sequential IM/oral ziprasidone vs haloperidol in severe schizophrenia. Eur Neuropsychopharmacol 2002;(Suppl 3):S291.
92. Brook S W. Sequential im/oral ziprasidone vs IM/oral haloperidol in patients with severe schizophrenia. Int J Neuropsychopharmacol 2002;(Suppl 1):S124.
93. Brook S W. Ziprasidone vs. haloperidol in sequential IM or oral treatment of acute schizophrenia. Schizophr Res 2002;(3 Suppl 1):181.
94. Brook S. Ziprasidone vs haloperidol in sequential IM/oral treatment of acute schizophrenia. Eur Neuropsychopharmacol 2001;(3):275.
95. Brown ES. Management of comorbid bipolar disorder and substance abuse. J Clin Psychiatry 2006;67(8):e05. PMID:17107268
96. Buchanan RW, Breier A, Kirkparrick B, et al. Clozapine versus haloperidol in the treatment of schizophrenic patients. J Am Osteopath Assoc 1998;98(7):366.
97. Buchsbaum MS, Potkin SG, Marshall JF, et al. Effects of clozapine and thiothixene on glucose metabolic rate in schizophrenia. Neuropsychopharmacology 1992;6(3):155-63. PMID:1599606
98. Buckley P. Comparison of the effect of quetiapine and haloperidol in a cohort of patients with treatment-resistant schizophrenia. Proceedings of the 7th World Congress of Biological Psychiatry 2001;(Suppl 1).
99. Buckley PF, Goldstein JM, Emsley RA. Comparison of quetiapine and haloperidol in treatment-resistant schizophrenia. Proceedings of the 154th Annual Meeting of the American Psychiatric Association 2001.
100. Bushe C, Leonard B. Association between atypical antipsychotic agents and type 2 diabetes: review of prospective clinical data. Br J Psychiatry 2004;184(Suppl47):s87-s93. PMID:15056600
101. Bushe CJ, Leonard BE. Blood glucose and schizophrenia: a systematic review of prospective randomized clinical trials. J Clin Psychiatry 2007;68(11):1682-90. PMID:18052561
102. Bustillo J. Differential brain effects of chronic exposure to haloperidol and quetiapine in antipsychotic-naive schizophrenia: a longitudinal protonmagnetic resonance spectroscopy study. Schizophr Res 2001;49(1,2):192.
103. Bustillo JR, Lauriello J, Rowland LM, et al. Effects of chronic haloperidol and clozapine treatments on frontal and caudate neurochemistry in schizophrenia. Psychiatry Res 2001;107(3):135-49. PMID:11566430
104. Caccia S, Pasina L, Nobili A. New atypical antipsychotics for schizophrenia: Iloperidone. Drug Des Dev Ther 2010;(4):33-48. PMID:20368905
105. Campbell DB, Ebert PJ, Skelly T, et al. Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. Biol Psychiatry 2008;63(1):32-41. PMID:17588543
106. Canas F, Perez-Sola V, Diaz S, et al. Cost-effectiveness analysis of ziprasidone versus haloperidol in sequential intramuscular/oral treatment of exacerbation of schizophrenia: economic subanalysis of the ZIMO trial. Clin Drug Invest 2007;27(9):633-45. PMID:17705572
107. Cantillon M. Quetiapine fumarate reduces aggression conference abstract. 11th Annual Meeting of the American Association for Geriatric Psychiatry 1998.

108. Cardoni AA. Risperidone: review and assessment of its role in the treatment of schizophrenia. Ann Pharmacother 1995;29(6):610-8. PMID:7545034
109. Carlson CD, Cavazzoni PA, Berg PH, et al. An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 2003;64(8):898-906. PMID:12927004
110. Carman J, Peuskens J, Vangeneugden A. Risperidone in the treatment of negative symptoms of schizophrenia: a meta-analysis. Int Clin Psychopharmacol 1995;10(4):207-13. PMID:8748041
111. Carson WH, Ali M. A double-blind, placebo-controlled trial of aripiprazole and haloperidol in patients with schizophrenia or schizoaffective disorder. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology 2000:14.
112. Carson WH, Kane JM. Efficacy of aripiprazole in psychotic disorders: comparison with haloperidol and placebo. Eur Neuropsychopharmacol 2000;10(Suppl3):S309.
113. Carson WH, Pigott TA, Saha AR. Aripirazole versus placebo in the treatment of chronic schizophrenia [poster]. XXIII Collegium Internationale Neuro-Psychopharmacologium (CINP) Congress, Montreal 2002.
114. Casademont J, Garrabou G, Miro O, et al. Neuroleptic treatment effect on mitochondrial electron transport chain: peripheral blood mononuclear cells analysis in psychotic patients. J Clin Psychopharmacol 2007;27(3):284-8. PMID:17502776
115. Casey DE. Implications of the CATIE trial on treatment: extrapyramidal symptoms. CNS Spectr 2006;11(7:Suppl 7):25-31. PMID:16816797
116. Cavazzoni P, Mukhopadhyay N, Carlson C, et al. Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications. Br J Psychiatry Suppl 2004;47:S94-101. PMID:15056601
117. Cavazzoni P. An integrated analysis of treatment-emergent extrapyramidal syndrome in schizophrenic patients during olanzapine clinical trials versus placebo, haloperidol, risperidone or clozapine. Schizophr Res 2002;(3 Suppl 1):171.
118. Cavazzoni PA, Berg PH, Kryzhanovskaya LA, et al. Comparison of treatment-emergent extrapyramidal symptoms in patients with bipolar mania or schizophrenia during olanzapine clinical trials. J Clin Psychiatry 2006;67(1):107-13. PMID:16426096
119. Cavezzoni P. An integrated analysis of treatment-emergent extrapyramidal syndrome in schizophrenic patients during olanzapine clinical trials versus placebo, haloperidol, ri. Int J Neuropsychopharmacol 2002;(Suppl 1):S164.
120. Centorrino F. Drug attitudes and treatment adherence in a clinical trial comparing haloperidol and olanzapine in first episode schizophrenia. Schizophr Res 2003.
121. Central SU. Efficacy and safety of risperidone oral solution combination clonazepam versus haloperidol intramuscular (IM) injection for treatment of acute psychotic agitation in schizophrenia. http://www.clinical.trials.gov
122. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158(4):518-26. PMID:11282684
123. Chakrabarti A, Bagnall A, Chue P, et al. Loxapine for schizophrenia. Cochrane Database Syst Rev 2007;(4):CD001943. PMID:17943763
124. Chaudhry HR, Kongsakon R. I. Quality of life and clinical outcomes for Asian outpatients with schizophrenia: a double-blind randomised comparison of olanzapine and haloperidol. Eur Neuropsychopharmacol 2003;(4):S309.
125. Cheer SM, Wagstaff AJ. Quetiapine: a review of its use in the management of schizophrenia. CNS Drugs 2004;18(3):173-99. PMID:14871161
126. Cheine MV, Wahlbeck K, Rimon R. Pharmacological treatment of schizophrenia resistant to first-line treatment: a critical systematic review and meta-analysis. Int J Psychiatr Clin Pract 1999;3(3):159-69.
127. Choi KH, Higgs BW, Weis S, et al. Effects of typical and atypical antipsychotic drugs on gene expression profiles in the liver of schizophrenia subjects. BMC Psychiatry 2009;9:57. PMID:19758435
128. Chouinard G, Albright PS. Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. J Clin Psychopharmacol 1997;17(4):298-307. PMID:9241010
129. Cipriani A, Rendell JM, Geddes J. Haloperidol alone or in combination for acute mania [systematic review]. Cochrane Database Syst Rev 2009;2009(1) PMID:16856043
130. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. Neuropsychiatr Dis Treat 2006;2(4):427-43. PMID:19412492
131. Citrome L. Interpreting and applying the CATIE results: With CATIE, context is key, when sorting out Phases 1, 1A, 1B, 2E, and 2T. Psychiatry (USA) 2007;4(10):23-9. PMID:20428308
132. Clouth J. Pharmacoeconomic evaluation of the treatment of schizophrenia in Germany: a comparison of olanzapine and haloperidol. Proceedings of the 152nd Annual Meeting of the American Psychiatric Association 1999;20.
133. Cohen D, Correll C, de HM. Do antipsychotic medications reduce or increase mortality in schizophrenia?: a critical apprisal of the FIN-11 study. Schizophr Res 2010;270.

134. Coleman CI, White CM. The impact of antipsychotic agent choice on the risk of coronary heart disease mortality due to cholesterol effects. Formulary 2007;42(1):62-5.
135. Conley RR, Tamminga CA, Beasley. Olanzapine vs chlorpromazine in therapy related-refractory schizophrenia. Schizophrenia Research (Special Issue) - The VIth International Congress on Schizophrenia Research 1997.
136. Conley RR, Tamminga CA, Beasley. Olanzapine vs chlorpromazine in therapy-refractory schizophrenia. Schizophr Res 1997;24(1,2):190.
137. Conley RR, Tamminga CA, Beasley. Olanzapine vs. chlorpromazine in treatment-resistant schizophrenia. Biol Psychiatry 1997;41:73S.
138. Conley RR. New antipsychotic strategies: quetiapine and risperidone vs. fluphenazine in treatment resistant schizophrenia. http://www.clinicaltrials.gov/
139. Conte G. Long-term risperidone versus haloperidol plus mood stabilisers in psychotic bipolar disorder. Int J Neuropsychopharmacol 2002;(Suppl 1):S109.
140. Conus P. Comparison of combination olanzapine and lithium and combination chlorpromazine and lithium in the treatment of a first manic episode with psychotic features. www.Controlled-Trials.com/
141. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161(3):414-25. PMID:14992963
142. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 2009;35(2):443-57. PMID:18417466
143. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 2008;21(2):151-6. PMID:18332662
144. Coulouvrat C, Dondey-Nouvel L. Safety of amisulpride (Solian): a review of 11 clinical studies. Int Clin Psychopharmacol 1999;14(4):209-18. PMID:10468313
145. Crawford AMK, Gomez JC, Beasley CM, et al. Olanzapine versus haloperidol: analysis of schizophrenic patients from the multi-center international trial. Eur Neuropsychopharmacol 1999;9(5):276.
146. Crocket G. Risperidone versus haloperidol in the treatment of chronic schizophrenic patients: UK centres in an international dose finding study. Proceedings of the 18th Collegium Internationale Neuro-Psychopharmacologicum Congress 1992;(Suppl 1):197.
147. Csernansky J. A long term double blind comparison of risperidone and haloperidol in stable outpatients with schizophrenia or schizoaffective disorder. Int J Neuropsychopharmacol 2000;(Suppl 1):S155.
148. Csernansky J. Risperidone vs haloperidol: relapse prevention in schizophrenia. XI World Congress of Psychiatry , Hamburg, August 6-11, 2000.
149. Csernansky JG, Okamoto A, Brecher MB. Risperidone versus haloperidol for prevention of relapse in schizophrenia and schizoaffective disorder: a long-term, double-blind comparison. Proceedings of the 51st Institute on Psychiatric Services 1999;110.
150. Csernansky JG, Okamoto A. Risperidone versus haloperidol for prevention of relapse in patients with schizophrenia and schizoaffective disorder: a long-term double blind comparison. Proceedings of the 38th Annual Meeting of the American College of Neuropsychopharmacology 1999;16.
151. Csernansky JG, Okamoto A. Risperidone vs haloperidol for relapse prevention in schizophrenia and schizoaffective disorder: a long-term double-blind comparison. Biol Psychiatry 2000;32S.
152. Csernansky JG, Okamoto A. Risperidone vs haloperidol: prevention of relapse in schizophrenia. Eur Neuropsychopharmacol 1999.
153. Cucchiaro J. A randomized, double-blind, multicenter phase iii study of iloperidone versus haloperidol and placebo in patients with schizophrenia or schizoaffective disorder. Schizophr Res 2001;(1,2):223-4.
154. Cuesta MJ, Peralta V, Zarzuela A. Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. Schizophr Res 2001;48(1):17-28. PMID:11278151
155. Czekalla J, Beasley CM, Jr., Dellva MA, et al. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. J Clin Psychiatry 2001;62(3):191-8. PMID:11305706
156. Czekalla J. Olanzapine versus haloperidol: a randomized, double-blind cross over study with 31p-nuclear magnetic resonance spectroscopy MRS and regional cerebral blood flow measurements fMRI of the dorsolateral prefrontal cortex dlpfc in schizophrenics. Schizophr Res 2002;(3 Suppl 1):180.
157. Czobor P, Volavka J. Quantitative electroencephalogram examination of effects of risperidone in schizophrenic patients. J Clin Psychopharmacol 1993;13(5):332-42. PMID:7693770
158. Daniel DG, Stock EG, Wilber CH, et al. Intramuscular aripiprazole in acutely agitated psychotic patients. 157th Annual Meeting of the American Psychiatric Association, New York, USA 2004.
159. David AS, Adams C. Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes. Health Technol Assess (Rockv) 2001;5(34):1-61.
160. David SR, Meehan k. Intramuscular olanzapine versus intramuscular haloperidol and intramuscular placebo: an international double-blind study in acutely agitated patients with schizophrenia. Schizophr Res 2001;(1,2):224.

161. David SR, Purdon S, Jones BD, et al. Olanzapine versus risperidone versus haloperidol in early illness schizophrenia: education improves outcomes in MDD. 152nd Annual Meeting of the American Psychiatric Association 1999.
162. David SR, Taylor CC, Kinon BJ, et al. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. Clin Ther 2000;22(9):1085-96. PMID:11048906
163. Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST): correction. The American Journal of Psychiatry 2009;166(6):731. PMID:19369319
164. Davies A, Adena MA, Keks NA, et al. Risperidone versus haloperidol: meta-analysis of efficacy and safety. Clin Ther 1998;20(1):58-71. PMID:9522104
165. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Archives of General Psychiatry 2003;60(6):553-64. PMID:12796218
166. Davis JM, Chen N. Clinical profile of an atypical antipsychotic: risperidone. Schizophr Bull 2002;28(1):43-61. PMID:12047021
167. Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: combined results of the North American and international trials. J Clin Psychiatry 2001;62(10):757-71. PMID:11816864
168. Davis L. To determine if olanzapine is more cost effective than haloperidol for the treatment of schizophrenia: the clinical and economic impact of olanzapine in the treatment of schizophrenia. National Institutes of Health 2010;2001.
169. De CH, Claus A. Risperidone vs haloperidol in chronic schizophrenia: treatment outcome and correlates with VBR. Proceedings of the 17th Collegium Internationale Neuro-Psychopharmacologicum Congress; 2010;1990-14.
170. De CH, Malfroid M. Risperidone versus haloperidol in chronic schizophrenic patients: a 12 week multicenter double-blind parallel study. Psychopharmacology (Berl) 1988;(Suppl 1):348.
171. De HL, van BN. Olanzapine and haloperidol for residual symptoms. Am J Psychiatry 2005;162(7):1392-3. PMID:15994737
172. De HL, van BN. Olanzapine vs haloperidol for treatment of schizophrenia. JAMA 2004;291(9):1065-6. PMID:14996769
173. de HL, van Bruggen. Subjective experience and d2 receptor occupancy in patients with schizophrenia, treated with low dose olanzapine or haloperidol; a randomized double-blind study. Schizophr Res 2002;(3 Suppl 1):179.
174. de Oliveira I, Miranda-Scippa AM, de Sena EP, et al. Risperidone versus haloperidol in the treatment of schizophrenia: a meta-analysis comparing their efficacy and safety. J Clin Pharm Ther 1996;21(5):349-58.
175. de Oliveira I. Risperidone vs. haloperidol in the treatment of schizophrenia: a meta-analysis comparing their efficacy and safety. XXth Collegium Internationale Neuro-psychopharmacologicum 2006;Melbourne,Australia.
176. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther 2004;26(5):649-66. PMID:15220010
177. Dellva M, Satterlee W, Tran P, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in acute treatment. 9th European College of Neuropsychopharmacology Congress 1996.
178. Dellva MA, Beasley CM, Kuntz AJ, et al. What is the differential risk of tardive dyskinesia with the novel antipsychotic olanzapine? 11th Annual Meeting of the American Association for Geriatric Psychiatry 2000.
179. Den BJ, Westenberg HG, Jansen AA. Risperidone in the treatment of chronic schizophrenia: a double blind comparative study with haloperidol. Clin Neuropharmacol 1992;15(Suppl 1 Pt B):118.
180. DeSilva P, Fenton M, Rathbone J. Zotepine for schizophrenia [systematic review]. Cochrane Database Syst Rev 2006;2009(1) PMID:17054149
181. Dillenschneider A. Comparison of intramuscular aripiprazole and haloperidol with placebo in acutely agitated schizophrenia patients. Eur Neuropsychopharmacol 2005;(Suppl.3):S509.
182. Dolnak DR, Minn K. Olanzapine versus haloperidol in the treatment of schizophrenia. Proceedings of the 149th Annual Meeting of the American Psychiatric Association; 2010;1996-9.
183. Dossenbach M, Treuer T, Kryzhanovskaya L, et al. Olanzapine versus chlorpromazine in the treatment of schizophrenia: a pooled analysis of four 6-week, randomized, open-label studies in the Middle East and North Africa. J Clin Psychopharmacol 2007;27(4):329-37. PMID:17632215
184. Dossenbach M. Olanzapine versus fluphenazine - six weeks treatment of acute schizophrenia. Proceedings of the 10th European College of Neuropsychopharmacology Congress; 2010;1997-17.
185. Dossenbach M. Sleep quality and early morning wakefulness of schizophrenic patients treated with olanzapine compared to chlorpromazine. Eur Neuropsychopharmacol 2000;(Suppl 3):S328-S329.
186. Duarte A. Risperidone vs haloperidol in schizophrenic patients: Argentine results. Proceedings of the 9th World Congress of Psychiatry; 1993;335.
187. Dubitsky GM, Harris R. Abilify (aripiprazole) tablets, medical review part 1. U S Food and Drug Administration CDER 2002;1-50.
188. Duggan L, Brylewski J. Antipsychotic medication for those with both schizophrenia and learning disability. Cochrane Database Syst Rev 2001;(3) PMID:11686948
189. Duggan L, Fenton M, Rathbone J, et al. Olanzapine for schizophrenia. Cochrane Database Syst Rev 2009;2009(4) PMID:15846619

190. Duncan E, Szilagyi S, Schwartz M, et al. Prepulse inhibition of acoustic startle in subjects with schizophrenia treated with olanzapine or haloperidol. Psychiatry Res 2003;120(1):1-12.
191. Duncan EJ, Woolson SL, Hamer RM, et al. Risk of lipid abnormality with haloperidol, olanzapine, quetiapine, and risperidone in a veterans affairs population. Int Clin Psychopharmacol 2009;24(4):204-13. PMID:19494785
192. Eli L. A double-blind dose-response study comparing short acting intramuscular olanzapine, short acting intramuscular haloperidol, and intramuscular placebo in patients with schizophrenia. http://wwwclinicalstudyresultsorg/ 2010.
193. Eli L. A double-blind randomized comparison of the efficacy and safety of intramuscular olanzapine and intramuscular haloperidol in acutely agitated patients with schizophrenia. http://www.clinicaltrials.gov/2010.
194. Eli L. A double-blind randomized comparison of the efficacy and safety of short acting intramuscular olanzapine, short acting intramuscular haloperidol and intramuscular placebo in patients with schizophrenia. http://wwwclinicalstudyresultsorg/ 2010.
195. Eli L. A fixed-dose range safety and efficacy study of olanzapine versus haloperidol in the treatment of schizophrenia. http://wwwclinicalstudyresultsorg/ 2010.
196. Eli L. Comparison of intramuscular olanzapine and intramuscular haloperidol in patients with schizophrenia. Eli Lilly and Company Clinical Trial Registry 2007;2004.
197. Eli L. Double-blind long-term study comparing the efficacy and safety of olanzapine versus haloperidol in patients with schizophrenia previously stabilized with conventional antipsychotic treatment. http://www.clinicaltrials.gov/2010.
198. Eli L. HGBQ: olanzapine versus haloperidol in partial responder schizophrenic patients. Data on file 2001;2001.
199. Eli L. Olanzapine versus haloperidol in the treatment of schizophrenia and other psychotic disorders. http://wwwclinicalstudyresultsorg/ 2010.
200. Eli L. Placebo- and haloperidol-controlled double-blind trial of olanzapine in patients with manic or mixed episode of bipolar I disorder. Controlled-Trials 2000;2006.
201. El-Sayeh HG, Morganti C, Adams CE. Aripiprazole for schizophrenia [systematic review]. Br J Psychiatry 2006;189:102-8. PMID:16880478
202. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev 2006;(2) PMID:16625607
203. Ely EW. Delirium in the ICU: a prospective, randomized, trial of placebo vs haloperidol vs ziprasidone. Clin Trials 2004;2004.
204. Emsley R, Oosthuizen P, Koen L, et al. Oral versus injectable antipsychotic treatment in early psychosis: post hoc comparison of two studies. Clin Ther 2008;30(12):2378-86. PMID:19167596
205. Emsley R, Oosthuizen P. Evidence-based pharmacotherapy of schizophrenia. Int J Neuropsychopharmacol 2004;7(2):219-38. PMID:15043765
206. Emsley R. Risk for akathisia in patients with recent onset schizophrenia treated with risperidone and haloperidol and its association with sucidality. Schizophr Res 2004;(1):183.
207. Emsley R. Risperidone in the treatment of first-episode patients with schizophreniform disorder: a double-blind multicenter study. 8th European College of Neuropsychopharmacology Congress 1995.
208. Emsley RA, Jones AM. Treatment of depressive symptoms in partially refractory schizophrenia: efficacy of quetiapine versus haloperidol. Eur Neuropsychopharmacol 2001;(3):264.
209. Essali A, Al-Haj HN, Li C, et al. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev 2009;2009(1) PMID:19160174
210. Essock SM, Frisman LK, Covell NH, et al. Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. Archives of General Psychiatry 2000;57(10):987-94. PMID:11015817
211. Fagiolini A, Goracci A. The long term maximising potential for rehabilitation in patients with schizophrenia. Eur Neuropsychopharmacol 2007;17(Suppl2):S123-S129. PMID:17336767
212. Farooq S, Sherin A. Interventions for psychotic symptoms concomitant with epilepsy [Systematic Review]. Cochrane Database Syst Rev 2011;(4) 2011;(4) PMID:18843704
213. Fenton M, Rathbone J, Reilly J, et al. Thioridazine for schizophrenia. Cochrane Database Syst Rev 2007;(3) PMID:17636691
214. Fischer-Barnicol D, Koch H, Lanquillon S, et al. The relevance of doses for comparing haloperidol, risperidone and olanzapine. Eur Psychiatry 2010;25(Suppl 1):992.
215. Fleischhacker W, Kahn R, Karayal O, et al. Eufest: the moderating impact of metabolic co-morbidities on treatment outcomes in first-episode schizophrenia. Eur Neuropsychopharmacol 2009;S529-S530.
216. Fleischhacker WW, Keet IP, Kahn RS, et al. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. Schizophr Res 2005;78(2-3):147-56. PMID:16055308
217. Fleischhacker WW, Linz CG, Hurst BC. Ici 204636 ('Seroquel'): a putative new atypical antipsychotic: results from phase iii trials conference proceeding. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia 2000;(132)
218. Fogelson DL, Sternbach H, Payne D. A naturalistic pilot study comparing haloperidol, clozapine, sertindole, and risperidone in partially responsive chronic schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1997;17(6):492-4. PMID:9408817

219. Fountoulakis, Konstantinos N, Vieta E. Efficacy and safety of aripiprazole in the treatment of bipolar disorder: a systematic review. Ann Gen Psychiatry 2009;8 PMID:19635147
220. Furtado VA, Srihari V, Kumar A. Atypical antipsychotics for people with both schizophrenia and depression [systematic review]. Cochrane Database Syst Rev 2010;2010(4) PMID:18254078
221. Gaebel W. One year maintenance treatment with low dose haloperidol vs risperidone in first-episode schizophrenia. http://www.clinicaltrials.gov/2010.
222. Gao K, Gajwani P, Elhaj O, et al. Typical and atypical antipsychotics in bipolar depression. J Clin Psychiatry 2005;66(11):1376-85. PMID:16420074
223. Gao K, Muzina D, Gajwani P, et al. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. J Clin Psychiatry 2006;67(9):1327-40. PMID:17017818
224. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999;156(8):1270-2. PMID:10450273
225. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ: British Medical Journal 2000;321(7273):1371-6. PMID:11099280
226. George M. A double-blind randomised comparison of the efficacy and safety of short acting intramuscular olanzapine, short acting intramuscular haloperidol and intramuscular placebo in patients with schizophrenia. National Research Register 2010.
227. Gharabawi G. Oral risperidone + lorazepam versus IM haloperidol + lorazepam in the emergency treatment of acute psychosis in schizophrenia and schizoaffective disorder. Schizophr Res 2003;60(Suppl 1):284.
228. Gharabawi GM, Bossie CA, Zhu Y. New-onset tardive dyskinesia in patients with first-episode psychosis receiving risperidone or haloperidol. Am J Psychiatry 2006;163(5):938-9. PMID:16648343
229. Gilmore JA, Kinon BJ, Zhao. Improvement in quality of life and depressive symptoms in schizophrenic patients is associated with robust acute treatment response of olanzapine versus haloperidol. Schizophr Res 2002;(3 Suppl 1):177.
230. Gilmore JA, Kinon BJ, Zhao. Rigorous criteria for treatment response differentiated efficacy of olanzapine versus haloperidol in patients with schizophrenia. Schizophr Res 2002;(3 Suppl 1):177.
231. Girardi P, Pompili M, Mosticoni S, et al. Intramuscular olanzapine: a critical-meta-analytic overview of some recent issues. Clin Neuropsychiatry J Treat Eval 2006;3(4):273-81.
232. Gismondi R. Aripiprazole versus perphenazine in treatment-resistant schizophrenia. XXIVth Collegium Internationale Neuro-Psychopharmacologicum Congress; 2010;2004.
233. Glazer WM, Johnstone BM. Pharmacoeconomic evaluation of antipsychotic therapy for schizophrenia. J Clin Psychiatry 1997;58(Suppl 4) PMID:9265917
234. Glazer WM. Expected incidence of tardive dyskinesia associated with atypical antipsychotics. J Clin Psychiatry 2000;61(Suppl 4):21-6. PMID:10739327
235. Glazer WM. Olanzapine vs haloperidol for treatment of schizophrenia. JAMA 2004;291(9):1064-5. PMID:14996766
236. Glick ID, Berg PH. Time to study discontinuation, relapse, and compliance with atypical or conventional antipsychotics in schizophrenia and related disorders. Int Clin Psychopharmacol 2002;17(2):65-8. PMID:11890188
237. Glick ID, Lemmens P, Vester-Blokland E. Treatment of the symptoms of schizophrenia: a combined analysis of double-blind studies comparing risperidone with haloperidol and other antipsychotic agents. Int Clin Psychopharmacol 2001;16(5):265-74. PMID:11552769
238. Glick ID, Shkedy Z, Schreiner A. Differential early onset of therapeutic response with risperidone vs conventional antipsychotics in patients with chronic schizophrenia. Int Clin Psychopharmacol 2006;21(5):261-6. PMID:16877896
239. Goeroecs T. Effects of aripiprazole and haloperidol on affective symptoms of schizophrenia: results from a long-term study. Proceedings of the World Psychiatric Association International Congress 2004.
240. Goldstein J. Efficacy and tolerability of quetiapine compared with haloperidol in schizophrenic patients partially responsive to conventional antipsychotic treatment. Proceedings of the 39th Annual Meeting of the New Clinical Drug Evaluation Unit; 1999;149.
241. Goldstein JM, Buckley P. Comparison of the effects of quetiapine and haloperidol in a cohort of patients with treatment-resistant schizophrenia. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology; 2000.
242. Grainger D. Medical resource use and work and social outcomes for olanzapine compared with haloperidol in the treatment of schizophrenia. Proceedings of the 21st Collegium Internationale Neuro-Psychopharmacologicum Congress; 2010;1998-16.
243. Green A. Comorbid substance use disorder and first episode schizophrenia: acute effects of olanzapine versus haloperidol. Schizophr Res 2001;(2 Suppl 1):230.
244. Gregor KJ, Hamilton SH, Edgell ET. Functional outcomes in schizophrenia: a European comparison of olanzapine and haloperidol. Schizophr Res 2000;(1):189.
245. Guilera G, Pino O, Gomez-Benito J, et al. Antipsychotic effects on cognition in schizophrenia: a meta-analysis of randomised controlled trials. Eur J Psychiatr 2009;23(2):77-89.
246. Gunasekara NS, Spencer CM, Keating GM. Spotlight on ziprasidone in schizophrenia and schizoaffective disorder. CNS Drugs 2002;16(9):645-52. PMID:12153335
247. Gunasekara NS, Spencer CM, Keating GM. Ziprasidone: a review of its use in schizophrenia and schizoaffective disorder. Drugs 2002;62(8):1217-51. PMID:12010089

248. Gurovich I, Vempaty A, Lippmann S. QTc prolongation: chlorpromazine and high-dosage olanzapine. Can J Psychiatry 2003;48(5):348. PMID:12866343
249. Haddad PM, Taylor M, Niaz OS. First-generation antipsychotic long-acting injections v. oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. Br J Psychiatry 2009;195(Suppl 52):s20-s28. PMID:19880913
250. Haffmans J. Effect of risperidone versus haloperidol on sleep in schizophrenics. Proceedings of the 11th Congress of the Association of European Psychiatrists; 2002;(Suppl 1):181s.
251. Haffmans J. The effect of risperidone versus haloperidol on sleep patterns of schizophrenic patients - results of a double-blind, randomised pilot trial. Eur Neuropsychopharmacol 2002;(Suppl 3):S268.
252. Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59(6):294-9. PMID:9671341
253. Hamann J, Kissling W, Leucht S, et al. New generation antipsychotics for first episode schizophrenia [systematic review]. Cochrane Database Syst Rev 2009;2009(1)
254. Hamilton SH, Breier A, David S. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. Eur Neuropsychopharmacol 1998;8(Suppl 2):S228.
255. Hamilton SH, Genduso LA, Revicki DA. Medical resource use and work and social outcomes for olanzapine compared with haloperidol in the treatment of schizophrenia and other psychotic disorders. Schizophr Res 1998;29(1-2):148.
256. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. Schizophr Res 2005;73(2-3):139-45. PMID:15653256
257. Herrera M. Double-blind study with risperidone vs haloperidol in schizophrenic patients with agitation and/or aggression P091. Proceedings of the XIII World Congress of Psychiatry 2005; 15.
258. Hirsch S P. A 28-week comparison of flexible-dose ziprasidone with haloperidol in outpatients with stable schizophrenia. World Congress of Psychiatry, Hamburg 1999.
259. Hong W. Reduction of the positive symptoms of schizophrenia by (ICI 204,636): results from phase II and III clinical trials. 9th European College of Neuropsychopharmacology Congress 1996.
260. Hong X, Wang X. Agranulocytosis and neutropenia with typical and atypical neuroleptics. Am J Psychiatry 2001;158(10):1736-7. PMID:11579015
261. Honigfeld G, Patin J. Predictors of response to clozapine therapy. Psychopharmacology (Berl) 1989;99(Suppl 7) PMID:2813666
262. Hosalli, Prakash, Davis JM. Depot risperidone for schizophrenia [systematic review]. Cochrane Database Syst Rev 2003;2009(1) PMID:14584007
263. Houston JP, Adams DH, Kirkwood SC, et al. Neuroreceptor gene polymorphisms and olanzapine depressive symptom response in schizophrenia. J Clin Psychopharmacol 2007;27(5):520-3. PMID:17873692
264. Houston JP, Kaiser C. Suicideal ideation changes in olanzapine- or haloperidol-treated patients with schizophrenia. 156th Annual Meeting of the American Psychiatric Association, San Francisco CA 2003.
265. Houthoofd SA, Morrens M, Sabbe BG. Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. Clin Ther 2008;30(9):1565-89. PMID:18840365
266. Hoyberg OJ, Fensbo C, Remvig J, et al. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. Acta Psychiatr Scand 1993;88(6):395-402. PMID:7508675
267. Hugenholtz GW, Heerdink ER, Stolker JJ, et al. Haloperidol dose when used as active comparator in randomized controlled trials with atypical antipsychotics in schizophrenia: comparison with officially recommended doses. J Clin Psychiatry 2006;67(6):897-903. PMID:16848649
268. Hunter RH, Joy CB, Kennedy E, et al. Risperidone versus typical antipsychotic medication for schizophrenia. Cochrane Database Syst Rev 2003;(2) PMID:12804396
269. Hurst BC, Link CG. A comparison of the tolerance profile of Seroquel(tm) with typical neuroleptics and placebo. Xth World Congress of Psychiatry, Madrid, Spain 23rd-28th August 1996.
270. Hwang TJ. IM olanzapine versus IM haloperidol plus lorazepam for acute agitation in schizophrenia. http://www.clinicaltrials.gov/
271. Ibrahim H. A functional MRI study of the neurocognitive effects of quetiapine compared to haloperidol in schizophrenia. Schizophr Bull 2007;(2):371.
272. Ibrahim H. Comparison of the neurocognitive effects of quetiapine and haloperidol in patients with schizophrenia: a functional mri study. Proceedings of the 160th Annual Meeting of the American Psychiatric Association 2007;24.
273. Inada T, Beasley CM, Jr., Tanaka Y, et al. Extrapyramidal symptom profiles assessed with the Drug-Induced Extrapyramidal Symptom Scale: comparison with Western scales in the clinical double-blind studies of schizophrenic patients treated with either olanzapine or haloperidol. Int Clin Psychopharmacol 2003;18(1):39-48.
274. Iskedjian M, Hux M, Remington GJ. The Canadian experience with risperidone for the treatment of schizophrenia: an overview. J Psychiatry Neurosci 1998;23(4):229-39. PMID:9785702
275. Janicak PG, Davis JM, Kasckow JW, et al. Risperidone versus haloperidol for schizoaffective disorder. Proceedings of the 152nd Annual Meeting of the American Psychiatric Association 1999;20.

276. Janicak PG, Glick ID, Marder SR, et al. The acute efficacy of aripiprazole across the symptom spectrum of schizophrenia: a pooled post hoc analysis from 5 short-term studies. J Clin Psychiatry 2009;70(1):25-35. PMID:19192472
277. Janicak PG, Keck P. Double-blind, randomized study of risperidone vs haloperidol for schizoaffective disorder. Proceedings of the 38th Annual Meeting of the American College of Neuropsychopharmacology 1999;16.
278. Janknegt R, Derijks L, Becker HE, et al. Antipsychotic agents in the treatment of schizophrenia: drug selection by means of the SOJA method. J Drug Assess 2002;5(3):S1-S30.
279. Janssen LP. A comparison of risperidone and haloperidol for prevention of relapse in subjects with schizophrenia and schizoaffective disorders. http://www.clinicaltrials.gov/.
280. Janssen. Risperidone in the treatment of chronic schizophrenic patients: an international multicentre double-blind parallel-group comparative study versus haloperidol. http://www.clinicaltrials.gov/.
281. Jerrell JM. Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications. Schizophr Bull 2002;28(4):589-605. PMID:12795493
282. Johnsen E, Jorgensen HA. Effectiveness of second generation antipsychotics: a systematic review of randomized trials. BMC Psychiatry 2008;8:31. PMID:18439263
283. Johnson AL, Johnson DAW, Peuskens J. Peer review of 'Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol'. Br J Psychiatry 1995;166:727-33.
284. Johnstone BM, Obenchain RL, Edgell ET, et al. Intent-to-treat analysis of repeated measures data from a randomized clinical trial comparing the cost and effectiveness of treatment for schizophrenia with olanzapine or haloperidol. 11th European College of Neuropsychopharmacology Congress 1998.
285. Joint formulary committee. British National Formulary 49th edition. 2011. Available from: URL: http:// www. bnf.org/
286. Jones B, Taylor CC, Meehan K. The efficacy of a rapid-acting intramuscular formulation of olanzapine for positive symptoms. J Clin Psychiatry 2001;62(Suppl 4) PMID:11232747
287. Jones B. Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. Proceedings of the 151st Annual Meeting of the American Psychiatric Association; 1998.
288. Kabanov SO, Mosolov SN. Cognitive functioning under treatment with risperidone and haloperidol in acute phase of schizophrenia. Schizophr Res 2002;(3 Suppl 1):193-4.
289. Kando JC, Shepski JC, Satterlee W, et al. Olanzapine: a new antipsychotic agent with efficacy in the management of schizophrenia. Ann Pharmacother 1997;31(11):1325-34. PMID:9391688
290. Kane J. Aripiprazole in treatment-resistant schizophrenia: a 6-week double- blind comparison study versus perphenazine. Schizophr Res 2004;(1):155-6.
291. Kane JM, Barnes TR, Correll CU, et al. Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials. J Psychopharmacol 2010;24(7):1019-29. PMID:20008446
292. Kane JM, Crandall DT, Marcus RN, et al. Symptomatic remission in schizophrenia patients treated with aripiprazole or haloperidol for up to 52 weeks. Schizophr Res 2007;95(1-3):143-50. PMID:17644313
293. Kane JM, Fleischhacker WW, Hansen L, et al. Akathisia: an updated review focusing on second-generation antipsychotics. J Clin Psychiatry 2009;70(5):627-43. PMID:19389331
294. Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol 2008;28(2:Suppl 1):29-35. PMID:18334910
295. Kane JM, Suncao-Talbott S, Eudicone JM, et al. The efficacy of aripiprazole in the treatment of multiple symptom domains in patients with acute schizophrenia: a pooled analysis of data from the pivotal trials. Schizophr Res 2008;105(1-3):208-15. PMID:18790605
296. Kane JM, Swyzen W, Wu X, et al. Long-term symptomatic remission in schizophrenia patients treated with aripiprazole or haloperidol. Proceedings of the 159th Annual Meeting of the American Psychiatric Association; 2006.
297. Kane JM, William HCJ, Kujawa MJ, et al. Aripiprazole vs perphenazine in treatment-resistant schizophrenia. Proceedings of the 156th Annual Meeting of the American Psychiatric Association 2003;22.
298. Kane JM. Aripiprazole versus perphenazine in treatment-resistant schizophrenia. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA 2003.
299. Kasper S, Tauscher J, Kufferle B, et al. Sertindole and dopamine D2 receptor occupancy in comparison to risperidone, clozapine and haloperidol: a 123I-IBZM SPECT study. Psychopharmacology (Berl) 1998;136(4):367-73. PMID:9600582
300. Keck PE, Reeves KR. The efficacy of ziprasidone in schizophrenia and schizoaffective disorder: an update. Sixth World Congress of Biological Psychiatry, Nice, France 1998;June:22-7.
301. Keshavan MS, Schooler NR, Sweeney JA, et al. Research and treatment strategies in first-episode psychoses: the Pittsburgh experience. Br J Psychiatry Suppl 1998;172(33):60-5. PMID:9764128
302. Khan A, Schwartz K, Stern C, et al. Mortality risk in patients with schizophrenia participating in premarketing atypical antipsychotic clinical trials. J Clin Psychiatry 2007;68(12):1828-33. PMID:18162012

303. Khanna S, Rajadhyaksha. Ziprasidone versus chlorpromazine in treatment-refractory schizophrenia. Schizophr Res 2003;290-1.
304. Kim JG, Cho DH, Lee SJ, et al. The comparison of efficacy between aripiprazole and haloperidol in treatment of chronic schizophrenia and schizoaffective disorder: results for 16-week clinical study. Eur Neuropsychopharmacol 2006;(Suppl 4):S417.
305. Kim JH, Byun HJ. Association of subjective cognitive dysfunction with akathisia in patients receiving stable doses of risperidone or haloperidol. J Clin Pharm Ther 2007;32(5):461-7. PMID:17875112
306. Kinon BJ, Basson MS, Tollefson GD. Gender-specific prolactin response to treatment with olanzapine versus haloperidol in schizophrenia. Proceedings of the 9th Biennial Winter Workshop on Schizophrenia; 1998;1998-13.
307. Kinon BJ, Chen L, Stauffer VL, et al. Early onset of antipsychotic action in schizophrenia: evaluating the possibility of shorter acute efficacy trials. J Clin Psychopharmacol 2010;30(3):286-9. PMID:20473064
308. Kinon BJ, scher-Svanum H, Adams DH, et al. The temporal relationship between symptom change and treatment discontinuation in a pooled analysis of 4 schizophrenia trials. J Clin Psychopharmacol 2008;28(5):544-9. PMID:18794651
309. Kleinberg DL, Davis JM, de CR, et al. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19(1):57-61. PMID:9934944
310. Knapp M, Windmeijer F, Brown J, et al. Cost-utility analysis of treatment with olanzapine compared with other antipsychotic treatments in patients with schizophrenia in the pan-European SOHO study. Pharmacoeconomics 2008;26(4):341-58. PMID:18370568
311. Ko G. Status report: ziprasidone conference abstract. Schizophrenia Research (The Vth International Congress on Schizophrenia Research), Wormsprings, VA USA 1995;(154)
312. Kopala L. EPS in recent onset schizophrenia: a comparison of risperidone and haloperidol. Proceedings of the 16th European College of Neuropsychopharmacology Congress 2003;24.
313. Kopala L. Extra-pyramidal signs and symptoms (EPS) in recent onset schizophrenia: a comparison of risperidone and haloperidol. Eur Neuropsychopharmacol 2003;(4):S338.
314. Kopala L. Extra-pyramidal signs and symptoms (EPS) in recent onset schizophrenia: a comparison of risperidone and haloperidol. Schizophr Res 2004;(1):187.
315. Korea HGFH. HGFH_Korea. Cochrane Schiphrenia Group 1989.
316. Kostakoglu E, Alptekin. Olanzapine vs. chlorpromazine- 6 weeks treatment of acute schizophrenia errata. Eur Neuropsychopharmacol 2001;(Suppl 3):S369.
317. Kostic D. Maintenance of response in chronic schizophrenia: effects of aripiprazole and haloperidol on affective symptoms. Schizophr Bull 2005;31(2):492.
318. Krakowski MI, Czobor P. Clozapine, olanzapine, and haloperidol treatment of violent patients with schizophrenia. 158th Annual Meeting of the American Psychiatric Association; 2005.
319. Kudo Y. Clinical trial of quetiapine in schizophrenia - efficacy and tolerability of quetiapine: a comparative double-blind study with masopramine in schizophrenic patients. Ann Meet World Psychiatr Assoc 1999.
320. Kujawa M, Saha AR, Ingenito GG. Aripiprazole for long-term maintenance treatment of schizophrenia [poster]. XXIII Collegium Internationale Neuro-Psychopharmacologium (CINP) Congress, Montreal 2002.
321. Kunz M. Olanzapine vs haloperidol for treatment of schizophrenia. JAMA 2004;291(9):1065-6.
322. Lahti AC, Holcomb HH, Weiler MA, et al. Changes rcbf after acute challenge with haloperidol and olanzapine in patients with schizophrenia conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe New Mexico USA 1999;17-21(224)
323. Lal S, Lal S. Chlorpromazine-induced cutaneous pigmentation: effect of replacement with clozapine. J Psychiatry Neurosci 2000;25(3):281. PMID:10863889
324. Lamberti JS, Crilly JF, Maharaj K, et al. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical antipsychotic drugs. J Clin Psychiatry 2004;65(5):702-6. PMID:15163259
325. Langbein K, Nenadic I, Rzanny R, et al. Differential effects of first- and second-generation antipsychotics on energy metabolism in frontal and temporal cortex of first-episode schizophrenia patients. Eur Arch Psychiatry Clin Neurosci 2009;S83.
326. Lauriello J. Longitudinal assessment of brain chemistry early in schizophrenia: a randomized controlled trial of quetiapine and haloperidol. Schizophr Bull 2005;31(2):444.
327. Lee JN, Yang BH, Nam CW. The influences of risperidone and clozapine on body weight and glucose level in patients with chronic schizophrenia: comparison with haloperidol. Eur Neuropsychopharmacol 2005;(Suppl.3):S457.
328. Lee M. Quetiapine is significantly superior to haloperidol and placebo in improving mood in patients with schizophrenia. Proceedings of the 7th World Congress of Biological Psychiatry; 2001;(Suppl 1):2001.
329. Lemieux AA, Goldman-Levine JD, Goren JL. Aripiprazole: an antipsychotic with a novel mechanism of action. J Pharm Technol 2003;19(6):365-72.

330. Lemmens P, Brecher M, Van BB. A combined analysis of double-blind studies with risperidone vs. placebo and other antipsychotic agents: factors associated with extrapyramidal symptoms. Acta Psychiatr Scand 1999;99(3):160-70. PMID:10100910
331. Lemmens P. Tolerability and cardiovascular safety of risperidone. Sixth World Congress of Biological Psychiatry, Nice, France 1998;June:22-7.
332. Leo R, Razzini C, Di LG, et al. Asymptomatic QTc prolongation during coadministration of aripiprazole and haloperidol. J Clin Psychiatry 2008;69(2):327-8. PMID:18363460
333. Leucht S, Barnes TRE, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. The American Journal of Psychiatry 2003;160(7):1209-22. PMID:12832232
334. Leucht S, Busch R, Kissling W, et al. Early prediction of antipsychotic nonresponse among patients with schizophrenia. J Clin Psychiatry 2007;68(3):352-60.
335. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373(9657):31-41. PMID:19058842
336. Leucht S, Engel RR, Bauml J, et al. Is the superior efficacy of new generation antipsychotics an artifact of LOCF? Schizophr Bull 2007;33(1):183-91.
337. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999;35(1):51-68. PMID:9988841
338. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003;361(9369):1581-9. PMID:12747876
339. Lewis R, Bagnall AM, Leitner M. Sertindole for schizophrenia [systematic review]. Cochrane Database Syst Rev 2005;2009(1)
340. Lewis SW, Davies L, Jones PB, et al. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. Health Technol Assess (Rockv) 2006;10(17):1-94. PMID:16707074
341. Licht RW, Bech P. How to manage mania not responding to a first-step 2 weeks treatment with quetiapine: a report from a prematurely discontinued randomised clinical trial. Acta Psychiatr Scand 2009;120(4):334-5. PMID:19689481
342. Licht RW. Typical and atypical antipsychotics in bipolar disorder. Acta Neuropsychiatr 2000;12(3):115-9.
343. Lieberman J. Olanzapine and haloperidol treatment of first epiode schizophrenia and schizoaffective disorder: 12 week outcome of a two year randomized double blind trial. Proceedings of the 2nd International Conference on Early Psychosis 2000.
344. Lieberman J. Remission in schizophrenia: a comparison of 2 dose regimens of ziprasidone versus haloperidol treatment in a 3-year double-blind extension study. Neuropsychopharmacology 2005;(Suppl 1):S197-S198.
345. Lieberman JA, Stroup TS, Mc Evoy JP, et al. Newer antipsychotics similar to older agents. J Fam Pract 2005;54(12):1026.
346. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol: correction. The American Journal of Psychiatry 2003;160(10):1901.
347. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001;11(1):25-32. PMID:11226809
348. Lima MS, de Jesus Mari. Quality of life of patients with schizophrenia: a randomized, naturalistic, controlled trial comparing olanzapine with typical antipsychotics in Brazil. 156th Annual Meeting of the American Psychiatric Association; San Francisco, USA 2003.
349. Lin CH, Kuo CC, Chou LS, et al. A randomized, double-blind, comparison of risperidone versus risperidone plus haloperidol treatment in schizophrenia. Eur Neuropsychopharmacol 2009;19(Suppl3):S256.
350. Lindborg SR, Beasley CM, Alaka K, et al. Effects of intramuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients. Psychiatry Res 2003;119(1-2):113-23. PMID:12860365
351. Lindenmayer J. A randomized, double-blind study of olanzapine vs haloperidol in the treatment of primary negative symptoms in schizophrenia. Schizophr Bull 2005;31(2):493-4.
352. Lindenmayer JP, Eerdekens E, Berry SA, et al. Safety and efficacy of long-acting risperidone in schizophrenia: a 12-week, multicenter, open-label study in stable patients switched from typical and atypical oral antipsychotics. J Clin Psychiatry 2004;65(8):1084-9.
353. Lindenmayer JP. Incidence of EPS with risperidone compared with haloperidol and placebo in patients with chronic schizophrenia. Proceedings of the 146th Annual Meeting of the American Psychiatric Association; 1993.
354. Lindner LM, Marasciulo AC, Farias MR, et al. Economic evaluation of antipsychotic drugs for schizophrenia treatment within the Brazilian Healthcare System. Rev Saude Publica 2009;43(Suppl 9) PMID:19669066
355. Lingjaerde O. Risperidone versus perphenazine in schizophrenia: a double-blind multicentre study. Clin Neuropharmacol 1992;(Suppl 1. Pt B):375b.

356. Lipkovich I, Baron D, Houston J, et al. Flexible-dose clinical trials: predictors and outcomes of antipsychotic dose adjustments. J Clin Psychopharmacol 2005;25(4):381-6. PMID:16012284
357. Litman RE, Hommer DW, Radant A, et al. Quantitative effects of typical and atypical neuroleptics on smooth pursuit eye tracking in schizophrenia. Schizophr Res 1994;12(2):107-20. PMID:8043521
358. Liu-Seifert H, Adams DH, Kinon BJ. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. BMC Med 2005;3:21. PMID:16375765
359. Loebel A. Predictors of long-term outcome in schizophrenia: a double-blind, 196-week study of ziprasidone and haloperidol. Schizophr Bull 2007;(2):442.
360. Loza N. Olanzapine compared to chlorpromazine in acute schizophrenia. Eur Neuropsychopharmacol 1999;(Suppl 5):S291.
361. Lu Y. Olanzapine in the treatment of schizoaffective disorder. 9th European College of Neuropsychopharmacology Congress 1996.
362. Lysaker PH. Olanzapine and risperidone may improve neurocognition more than haloperidol in people with schizophrenia who continue treatment for 52 weeks. Evid Based Ment Health 2006;(3):71. PMID:16868190
363. Magnus A, Carr V, Mihalopoulos C, et al. Assessing cost-effectiveness of drug interventions for schizophrenia. Aust NZ J Psychiatry 2005;39(1-2):44-54. PMID:15660705
364. Mahmoud RA, Engelhart LM. Risperidone versus conventional antipsychotics in usual care: a prospective randomised effectiveness trial of outcomes for patients with schizophrenia and schizoaffective disorder. 1998.
365. Mahmoud RA, Engelhart MA. Risperidone vs conventional antipsychotics in ususl care: a prospective randomized effectiveness trial of outcomes for patients with schizophrenia and schizoaffective disorder. 21st Collegium internationale neuro-psychopharmaclogicum congress 1998.
366. Mak KY, Ng S, Wong MC, et al. A cost-analysis of risperidone in the treatment of chronic schizophrenia with predominating negative symptoms in Hong Kong. Hong Kong J Psychiatr 2000;10(3):14-44.
367. Malhotra A. Symptomatic remission in schizophrenia patients treated with aripiprazole or haloperidol for up to 52 weeks. Neuropsychopharmacology 2005;(Suppl 1):S199-S200.
368. Malyarov S D. Comparative assessment of the positive and negative symptom dynamics in schizophrenic patients treated with atypical antipsychotics or haloperidol. Eur Neuropsychopharmacol 1999;S269.
369. Malyarov S D. Comparative assessment of the positive and negative symptom dynamics in schizophrenic patients treated with atypical antipsychotics or haloperidol. 1999 p. 296.
370. Malykhin N. Comparative efficacy of risperidone, clozapine and haloperidol in the treatment of schizoaffective disorders with manic symptoms. Eur Neuropsychopharmacol 2003;(4):S304.
371. Marazuela R, Rubio-Terres C, Giner J, et al. Pharmacoeconomic analysis of the treatment of schizophrenia with quetiapine, olanzapine, risperidone or haloperidol in Spain. J Med Econ 2006;9(101-119):101-19.
372. Marder S. Risperidone versus haloperidol versus placebo in the treatment of chronic schizophrenia. Clin Res Rep RIS-INT-3 1991;1991.
373. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58(12):538-46. PMID:9448657
374. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003;61(2-3):123-36. PMID:12729864
375. Marder SR, Wirshing WC, Glynn S, et al. Risperidone and haloperidol in maintenance treatment: Interactions with psychosocial treatments. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe New Mexico USA 1999;17-21(288)
376. Marder SR. Risperidone: efficacy. J Clin Psychiatr Monogr 1994;12(2):49-52.
377. Marino J, Caballero J. Iloperidone for the treatment of schizophrenia. Ann Pharmacother 2010;44(5):863-70. PMID:20388862
378. Martin JL, Perez V, Sacristan M, et al. Meta-analysis of drop-out rates in randomised clinical trials, comparing typical and atypical antipsychotics in the treatment of schizophrenia. Eur Psychiatry 2006;21(1):11-20. PMID:16380237
379. Martinez R. Risperidone versus haloperidol for prevention of relapse in schizohrenia and schizoaffective disorders. Schizophr Res 1999;1-3
380. Mattes JA. Risperidone: how good is the evidence for efficacy? Schizophr Bull 1997;23(1):155-61. PMID:9050121
381. Mattingly G, Hochfeld M, Meng X. Response rates with iloperidone among patients with schizophrenia: pooled date from 2 phase iii clinical trials. 2010. November 18-21, 2010, Orlando, Florida. United States Psychiatric and Mental Health Congress.
382. McEvoy J. Long-term efficacy and safety of atypical and conventional antipsychotic drugs in first episode schizophrenia. Schizophr Res 2003;60(1):313.
383. McGurk SR, Green MF, Wirshing WC, et al. The effects of risperidone vs. haloperidol on spatial working memory in treatment-resistant schizophrenia. Biol Psychiatry 1996;39(1):571.

384. McGurk SR, Green MF, Wirshing WC, et al. The effects of risperidone versus haloperidol on frontal lobe functioning in treatment-resistant schizophrenia. Proceedings of the 150th Annual Meeting of the American Psychiatric Association; 1997;1997-22.
385. McGurk SR, Green MF, Wirshing WC, et al. The effects of risperidone versus haloperidol on frontal lobe functioning in treatment-resistant schizophrenia. 150th Annual Meeting of the American Psychiatric Association 1998.
386. McQuade R. Efficacy and safety of aripiprazole versus perphenazine in treatment-resistant schizophrenia. Eur Neuropsychopharmacol 2003;(4):S326.
387. McQuade R. Intramuscular aripiprazole in acute schizophrenia: a double-blind, placebo-controlled comparison with IM haloperidol. Proceedings of the 13th Biennial Winter Workshop on Schizophrenia Research 2006;10.
388. Meibach RC. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. Neurology 2000;55(7):1069. PMID:11061283
389. Meltzer D. Remission in schizophrenia: a comparison of the cost-effectiveness of 2 dose regimens of ziprasidone versus haloperidol treatment in a 3-year double-blind extension study. Schizophr Bull 2007;(2):487.
390. Meltzer H, Cohen M, Snow-Adami L, et al. Long-term safety and maintenance of effect of asenapine in patients with acute exacerbation of schizophrenia. Eur Neuropsychopharmacol 2009;19(Suppl 3):S536-S537.
391. Meltzer HY, Kujawa MJ, Carson JWH, et al. Aripiprazole and perphenazine in severe treatment-resistant schizophrenia. Proceedings of the 157th Annual Meeting of the American Psychiatric Association 2004;6.
392. Meltzer HY. Dimensions of outcome with clozapine. Br J Psychiatry 1992;17:46-53. PMID:1418889
393. Mendelowitz AJ. The utility of intramuscular ziprasidone in the management of acute psychotic agitation. Ann Clin Psychiatry 2004;16(3):145-54. PMID:15517847
394. Messotten F. Risperidone versus haloperidol in the treatment of chronic psychotic patients: a multi center double-blind study. Cochrane Collaboration 1991.
395. Meyer JM, Davis VG, McEvoy JP, et al. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1. Schizophr Res 2008;103(1-3):104-9. PMID:18534821
396. Meyer JM, Nasrallah HA, McEvoy JP, et al. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial: clinical comparison of subgroups with and without the metabolic syndrome. Schizophr Res 2005;(1):9-18.
397. Miller DD, Eudicone JM, Pikalov A, et al. Comparative assessment of the incidence and severity of tardive dyskinesia in patients receiving aripiprazole or haloperidol for the treatment of schizophrenia: a post hoc analysis. J Clin Psychiatry 2007;68(12):1901-6. PMID:18162021
398. Miller DD, O'Leary DS, Andreasen NC. Comparison of the effect of haloperidol and risperidone on regional cerebral blood flow in schizophrenia conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research) 1999; 228.
399. Miller DD, O'Leary DS, Andreasen NC. Differences in the effect of risperidone and haloperidol on RCBF in patients with schizophrenia performing a practiced memory task. Schizophr Res 2001;(1,2):181-2.
400. Miller DD, Ziebell S, Nopoulos. Risperidone versus haloperidol in a prospective longitudinal follow-up of recent-onset schizophrenia schizophrenia. Schizophrenia Research (Special Issue) - The VIth International Congress on Schizophrenia Research), Colorado Springs, Colorado, USA 1997.
401. Mimica N. Olanzapine compared to fluphenazine in the treatment of schizophrenia conference presentation. Schizophrenia Research (9th Biennial Winter Workshop on Schizophrenia 1998;(150)
402. Modell S J. Efficacy of aripiprazole and perphenazine in severe schizophrenia resistant to treatment with atypical antipsychotics. Eur Neuropsychopharmacol 2004;(Suppl 3):S265.
403. Moller HJ. Amisulpride: a review of its efficacy in schizophrenia. Acta Psychiatr Scand Suppl 2000;400:17-22. PMID:10823307
404. Moller HJ. Management of the negative symptoms of schizophrenia: new treatment options. CNS Drugs 2003;17(11):793-823. PMID:12921492
405. Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. Br J Psychiatry 2003;183:161-6. PMID:12893670
406. Montero I, Talavera M, Ruiz I. Clinical trials with a new atypical antipsychotic (aripiprazole): Gender specific information analysis. Women Health 2008;47(4):39-51. PMID:18843939
407. Montgomery JH, Byerly M, Carmody T, et al. An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. Control Clin Trials 2004;25(6):598-612. PMID:15588746
408. Mullen B, Brar JS, Vagnucci AH, et al. Frequency of sexual dysfunctions in patients with schizophrenia on haloperidol, clozapine or risperidone. Schizophr Res 2001;48(1):155-8. PMID:11345946
409. Muller-Spahn F. Risperidone in the treatment of chronic schizophrenic patients: an international double-blind parallel-group study versus haloperidol. Clin Neuropharmacol 1992;15(Suppl 91A) PMID:1379882
410. Murasaki M. Clinical evaluation of quetiapine in schizophrenia: efficacy and tolerability of quetiapine compared with haloperidol in patients with schizophrenia. Proceedings of the 11th World Congress of Psychiatry 1999;11.
411. Murasaki M. Risperidone in the treatment of schizophrenia: a double-blind comparison with haloperidol. Eur Neuropsychopharmacol 1995;5(Supplement 1):350.

412. Murasaki M. Risperidone in the treatment of schizophrenia: a double-blind comparison with haloperidol. Proceedings of the 8th European College of Neuropsychopharmacology Congress; 1995;1995-Oct.
413. Murphy BP, Chung YC, Park TW, et al. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res 2006;88(1-3):5-25. PMID:16930948
414. Myers J. The long-term benefit of risperidone versus haloperidol for affective symptoms in schizophrenia and schizoaffective disorder. Schizophr Res 2001;(1,2):240.
415. Myers JE, Mahmoud RA, Keith SJ, et al. Long-term benefit of risperidone versus haloperidol for affective symptoms in patients with schizophrenia and schizoaffective disorder. 154th Annual Meeting of the American Psychiatric Association; 2001.
416. Nagao M. Quantitative electroencephalography in schizophrenia: therapeutic effects of haloperidol and risperidone. 11th European College of Neuropsychopharmacology Congress 1998.
417. Namjoshi M. Conical and quality-of-life outcomes associated with olanzapine, risperidone, and haloperidol treatment in patients with schizophrenia: results from a US random study. Int J Neuropsychopharmacol 2002;(Suppl 1):S127.
418. Namjoshi M. Cost-effectiveness of olanzapine compared to risperidone and haloperidol in the treatment of patients with schizophrenia: results from a U.S. randomized controlled trial. Schizophr Res 2003;60(Suppl 1):296.
419. Namjoshi M. Hospitalization rates associated with olanzapine, risperidone, and haloperidol treatment in patients with schizophrenia: results from a U.S. randomized controlled trial. Eur Neuropsychopharmacol 2002;(Suppl 3):S315.
420. Namjoshi M. Olanzapine versus haloperidol: improvements in quality of life and compliance with treatment in patients with bipolar disorder. 154th Annual Meeting of the American Psychiatric Association; 2001.
421. Namjoshi Madhav, Shi Lizheng, Zhang Fan, et al. Olanzapine versus haloperidol: improvements in quality of life and compliance with treatment in patients with bipolar disorder. 155th Annual Meeting of the American Psychiatric Association; 2002.
422. Nasrallah HA, Brecher M, Paulsson B. Placebo-level incidence of extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. Bipolar Disord 2006;8(5:Pt 1):74. PMID:17042884
423. Nasrallah HA, Rennie P. Patterns of response in patients with schizophrenia partially responsive to fluphenazine and switched to quetiapine or haloperidol. Eur Neuropsychopharmacol 2001;(3):262.
424. Nasrallah HA. Focus on lower risk of tardive dyskinesia with atypical antipsychotics. Ann Clin Psychiatry 2006;18(1):57-62. PMID:16517454
425. Nasrallah HA. Metabolic findings from the CATIE trial and their relation to tolerability. CNS Spectr 2006;11(Suppl 7):7-9. PMID:16816798
426. Naukkarinen H. Olanzapine and perphenazine in schizophrenia. Schizophr Res 2000;(1):190.
427. Nemeroff CB. Dosing the antipsychotic medication olanzapine. J Clin Psychiatry 1997;58(Suppl 9) PMID:9265916
428. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. Ann Pharmacother 2006;40(4):674-82. PMID:16569811
429. Nightengale BS, Garrett L, Waugh S, et al. Health economics: economic outcomes associated with the use of risperidone in a naturalistic group practice setting. Am J Managed Care 1998;4(3):360-6. PMID:10178498
430. O'Connor R. A 28-week comparison of flexible-dose ziprasidone with haloperidol in outpatients with stable schizophrenia: risperidone versus haloperidol for prevention of relapse in schizophrenia and schizoaffective disorders: a long-term, double-blind comparison. Proceedings of the 51st Institute on Psychiatric Services 1999;Nov.
431. Oh PI, Iskedjian M, Addis A, et al. Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis. Can J Clin Pharmacol 2001;8(4):199-206. PMID:11743592
432. Oh PI, Lanctot KL, Mittmann N, et al. Cost-utility of risperidone compared with standard conventional antipsychotics in chronic schizophrenia. J Med Econ 2001;4(137-156):137-56.
433. Olanzapine for injection: new formulation. Prescrire Int 2004;13(71):92-3.
434. Olfson M, Uttaro T, Carson WH, et al. Male sexual dysfunction and quality of life in schizophrenia. J Clin Psychiatry 2005;66(3):331-8. PMID:15766299
435. Oren D. Efficacy and safety of intramuscular aripiprazole, haloperidol or placebo in acutely agitated patients with schizophrenia or schizoaffective disorder. Schizophr Bull 2005;31(2):499.
436. Oren DA, Marcus RN, Manos. Non-inferiority of intramuscular aripiprazole versus intramuscular haloperidol for the treatment of agitation associated with schizophrenia/schizoaffective disorder. Schizophr Bull 2007;33(2):451.
437. Organon. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia. http://www.clinicaltrials.gov/2010.
438. Palmer CS, Brunner E, Ruiz-Flores LG, et al. A cost-effectiveness clinical decision analysis model for treatment of schizophrenia. Arch Med Res 2002;33(6):572-80. PMID:12505105
439. Parellada E. Clinical experience and management considerations with long-acting risperidone. Curr Med Res Opin 2006;22(2):241-55. PMID: 16466596

440. Parsons B, Allison DB, Loebel A, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophr Res 2009;110(1-3):103-10. PMID:19321312
441. Pathiraja AP, Diamond BI, Borison RL, et al. Relationship between creatine phosphokinase, psychotic symptoms and novel antipsychotic drugs conference abstract. Schizophrenia Research (The Vth International Congress on Schizophrenia Research), Wormsprings, VA USA 1995;15(1-2):160.
442. Pecenak J. Relapse prevention in schizophrenia: Evidence from long-term, randomized, double-blind clinical trials. Neuroendocrinol Lett 2007;28(Suppl 1):49-70. PMID:17262007
443. Pelayo-Teran JM, Perez-Iglesias R, Mata I, et al. Early response to antipsychotics as a marker of treatment response of psychosis. Schizophr Res 2010;180.
444. Peralta V, Campos MS, de Jalon EG, et al. DSM-IV catatonia signs and criteria in first-episode, drug-naive, psychotic patients: psychometric validity and response to antipsychotic medication. Schizophr Res 2010;118(1-3):168-75. PMID:20071147
445. Perez R. Efficacy and safety of olanzapine, risperidone and haloperidol in acute treatment of patients with first episode psychosis. Schizophr Res 2003;9
446. Peters P. A randomized, double blind, multi-center study to assess the antipsychotic and motor effects of acp-103 when administered in combination with haloperidol or risperidone to schizophrenic subjects. http://www.clinicaltrials.gov/
447. Petrie JL, Saha AR, McEvoy JP. Aripiprazole, a new typical antipsychotic: phase 2 clinical trial result. 10th European College of Neuropsychopharmacology Congress 1997.
448. Peuskens J, Moller HJ, Puech A. Amisulpride improves depressive symptoms in acute exacerbations of schizophrenia: comparison with haloperidol and risperidone. Eur Neuropsychopharmacol 2002;12(4):305-10. PMID:12126869
449. Peuskens J, Van BB, De SC, et al. Effects of risperidone on affective symptoms in patients with schizophrenia. Int Clin Psychopharmacol 2000;15(6):343-9. PMID:11110010
450. Peuskens J. Risperidone in the treatment of chronic schizophrenic patients: an international double blind parallel group comparative study versus haloperidol. Clin Report 1992;1992.
451. Pfizer. Ziprasidone intramuscular/oral versus haloperidol intramuscular/oral in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: a six week open administration study with blinded assessments. http://wwwclinicalstudyresultsorg/ 2010.
452. Pickar D, Owen RR, Litman RE, et al. Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. Archives of General Psychiatry 1992;49(5):345-53. PMID:1375019
453. Pini S, Abelli M, Cassano GB. The role of quetiapine in the treatment of bipolar disorder. Expert Opin Pharmacother 2006;7(7):929-40. PMID:16634715
454. Pivac N. The effects of olanzapine or fluphenazine on peripheral biochemical markers in schizophrenic patients. Int J Neuropsychopharmacol 2002;(Suppl 1):S184.
455. Plesnicar BK, Zalar B, Breskvar K, et al. The influence of the CYP2D6 polymorphism on psychopathological and extrapyramidal symptoms in the patients on long-term antipsychotic treatment. J Psychopharmacol 2006;20(6):829-33. PMID:16478753
456. Pogarell O, Juckel G, Mulert C, et al. EEG abnormalities under treatment with atypical antipsychotics: effects of olanzapine and amisulpride as compared to haloperidol. Pharmacopsychiatry 2004;37(6):304-5. PMID:15551199
457. Polsky D, Doshi JA, Bauer MS, et al. Clinical trial-based cost-effectiveness analyses of antipsychotic use. Am J Psychiatry 2006;163(12):2047-56. PMID:17151153
458. Postgraduate Medicine. Antipsychotics and diabetes: case reports and cohort studies. Postgrad Med 2003;114(Suppl 6):59-71.
459. Potkin SG, Gutierrez R. 150th Annual Meeting of the American Psychiatric Association; 1997 May 17-22nd; San Diego, California, USA 1997.
460. Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol 2008;28(Suppl 1):2-11. PMID:18334911
461. Potkin SG. Efficacy and safety of once-daily dosing with risperidone in patients with schizophrenia. 1997.
462. Purdon SE, Canadian CaOSG. Neuropsychological change in early phase schizophrenia over twelve months of treatment with olanzapine, risperidone, or haloperidol. Schizophr Res 1998;(1,2):152-3.
463. Purdon SE, Jones B. A multicentre comparison of olanzapine, risperidone, and haloperidol on working memory, new learning, and delayed recall of verbal and nonverbal materials in early-phase schizophrenia over a 12-month prospective double-blind clinical trial. Schizophr Res 1999;(1-3):150.
464. Purdon SE, Jones BDW, Stip E L. Olanzapine versus haloperidol versus risperidone in early illness schizophrenia. Data on File , 39-45. 2001.
465. Purdon SE, Malla A. Neuropsychological change in schizophrenia after 6 months of double blind treatment with quetiapine or haloperidol. Schizophr Res 2000;(1):205-6. PMID:11291531
466. Rabinowitz J, Levine SZ, Barkai O, et al. Dropout rates in randomized clinical trials of antipsychotics: a meta-analysis comparing first- and second-generation drugs and an examination of the role of trial design features. Schizophr Bull 2009;35(4):775-88. PMID:10711911
467. Ramey T. 12-week, double-blind, placebo-controlled study of ziprasidone vs haloperidol for efficacy and maintained treatment effect in acute bipolar mania. Neuropsychopharmacology 2004;S203.

468. Rappard F. Remission in schizophrenia: a comparison of 2 dose regimens of ziprasidone versus haloperidol in a 40-week core and 3-year double-blind continuation study. Eur Neuropsychopharmacol 2006;(Suppl 4):S390.
469. Rappard F. Remission in schizophrenia: a comparison of two dose regimens of ziprasidone versus haloperidol treatment in a three-year double blind extension study. Proceedings of the 19th European College of Neuropsychopharmacology Congress 2006;20.
470. Rasmussen M. The impact on long-term outcome of early intervention with risperidone or haloperidol in first episode psychosis: characteristics at baseline conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe New Mexico USA 1999;17-21(293)
471. Rathbone J, McMonagle T. Pimozide for schizophrenia or related psychoses [systematic review]. Cochrane Database Syst Rev 2007;2009(1)
472. Rendell JM, Gijsman HJ, Bauer MS, et al. Risperidone alone or in combination for acute mania [systematic review]. Cochrane Database Syst Rev 2006;2009(1)
473. Rendell JM, Gijsman HJ, Keck PK, et al. Olanzapine alone or in combination for acute mania [systematic review]. Cochrane Database Syst Rev 2009;2009(1)
474. Reveley M. Seroquel outcome study (SOS): a multicentre double-blind randomised trial to compare the effects of seroquel and chlorpromazine on treatment outcome of schizophrenic patients. National Research Register 2010.
475. Revicki D. Effect of olanzapine on deficit syndrome symptoms in chronic schizophrenia. 8th European College of Neuropsychopharmacology Congress 1995.
476. Revicki D. Olanzapine versus haloperidol therapy for chronic schizophrenia: impact on deficit syndrome. Eur Neuropsychopharmacol 1995;5(Suppl 1):347.
477. Revicki D. Quality of life outcomes for olanzapine and haloperidol treatment for schizophrenia and other psychotic disorders: results of an international randomized clinical trial. Qual Life Res 1996.
478. Revicki D. Quality of life outcomes for olanzapine and haloperidol treatment for schizophrenia and related psychotic disorders. Proceedings of the 149th Annual Meeting of the American Psychiatric Association; 1996;1996-9.
479. Richardson CM, Kelly DL, old JM, et al. Risperidone vs quetiapine vs fluphenazine in treatment-resistant schizophrenia: neuropsychological outcome. Schizophr Bull 2005;31(2):501-2.
480. Rimon R. Olanzapine versus perphenazine in the treatment of schizophrenia: a double-blind study. Schizophr Res 2004;(1):164-5.
481. Rodova A, Svestka J, Nahunek K, et al. A blind comparison of clozapine and perphenazine in schizophrenics. Act Nerv Super (Praha) 1973;15(2):94-5.
482. Rosenheck R, Cramer J, Allan E, et al. Cost-effectiveness of clozapine in patients with high and low levels of hospital use. Archives of General Psychiatry 1999;56(6):565-72. PMID:10359474
483. Rosenheck R, Cramer J, Xu W, et al. Multiple outcome assessment in a study of the cost-effectiveness of clozapine in the treatment of refractory schizophrenia on Clozapine in Refractory Schizophrenia. Health Serv Res 1998;33(5:Pt 1):-1261. PMID:9865219
484. Rosenheck R, Doyle J, Leslie D, et al. Changing environments and alternative perspectives in evaluating the cost-effectiveness of new antipsychotic drugs. Schizophr Bull 2003;29(1):81-93. PMID:12908663
485. Rosenheck RA, Leslie DL, Sindelar J, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry 2006;163(12):2080-9. PMID:17151158
486. Rosenheck RA. Aripiprazole and perphenazine: no difference. J Clin Psychiatry 2000;68(11):1812-3. PMID:18052580
487. Rosenheck RA. Effectiveness versus efficacy of second-generation antipsychotics: haloperidol without anticholinergics as a comparator. Psychiatric Services 2005;56(1):85-92. PMID:15637198
488. Sa AR, Hounie AG, Sampaio AS, et al. Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol. Compr Psychiatry 2009;50(5):437-42. PMID:19683614
489. Sanchez R. Aripiprazole versus perphenazine in treatment-resistant schizophrenia. Schizophr Bull 2005;31(2):502.
490. Sanger T. A controlled study on the course of primary and secondary negative symptoms conference abstract. 150th Annual Meeting of the American Psychiatric Association 1997.
491. Sanger TM, Lieberman JA, Tohen. Olanzapine versus haloperidol in the treatment of first episode psychosis. Schizophrenia Research (9th Biennial Winter Workshop on Schizophrenia 1998;151.
492. Satterlee W. Olanzapine, a new "atypical" antipsychotic. Schizophrenia Research (The Vth International Congress on Schizophrenia Research), Wormsprings, VA USA 1995;(163)
493. Sauriol L, Laporta M, Edwardes MD, et al. Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach. Clin Ther 2001;23(6):942-56. PMID:11440294
494. Schausberger B. Impact of olanzapine versus fluphenazine on patient's drug acceptance during acute treatment of schizophrenia. Eur Neuropsychopharmacol 1992.
495. Schennach-Wolff R, Jager M, Mayr A, et al. Early response and its predictive validity within a randomised double-blind 1 year follow-up trial. Eur Arch Psychiatry Clin Neurosci 2009;S57.

496. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. Archives of General Psychiatry 2007;64(4):442-55. PMID:17404121
497. Schooler N. Reduced relapse rates in recent onset schizophrenia patients treated with risperidone vs. haloperidol. Eur Neuropsychopharmacol 2003;(4):S337.
498. Schooler NN. The efficacy and safety of conventional and atypical antipsychotics in first-episode schizophrenia: a review of the literature. Clin Schizophr Relat Psychoses 2007;1(1):27-42.
499. Schulz S. Efficacy of quetiapine compared with haloperidol and placebo in the short-term treatment of acute schizophrenia. Eur Neuropsychopharmacol 2000;(Suppl 3):302-3.
500. Schulz S. Efficacy of quetiapine versus haloperidol and placebo in the short-term treatment of acute schizophrenia. 153rd Annual Meeting of the American Psychiatric Association Chicago, Illionois, USA 2000.
501. Schulz SC, Thomson R, Brecher M. The efficacy of quetiapine vs haloperidol and placebo: a meta-analytic study of efficacy. Schizophr Res 2003;62(1-2):1-12. PMID:12765737
502. Scott LJ. Iloperidone: in schizophrenia. CNS Drugs 2009;23(10):867-80. PMID:19739696
503. Sharma T. A multi-centre, double-blind, randomised trial to compare the effects of "seroquel" and haloperidol in schizophrenic patients with a history of partial response to antipsychotic treatment. National Research Register 2001.
504. Sherwood M, Thornton AE, Honer WG. A meta-analysis of profile and time-course of symptom change in acute schizophrenia treated with atypical antipsychotics. Int J Neuropsychopharmacol 2006;9(3):357-66. PMID:16316478
505. Shi L. Olanzapine versus haloperidol as initial treatment in acute mania: prospective comparison of work functional outcomes. Int J Neuropsychopharmacol 2002;(Suppl 1):108.
506. Shi Lizheng, Namjoshi Madhav, Tohen Mauricio. Olanzapine versus haloperidol: a prospective comparison of clinical and humanistic outcomes in bipolar disorder. 155th Annual Meeting of the American Psychiatric Association; 2002.
507. Shim JC, Choe BM, Kim JG, et al. Discontinuation of risperidone, olanzapine, and haloperidol in first-episode psychosis. J Clin Psychopharmacol 2007;27(4):400-1. PMID:17632229
508. Si T. Multicenter, open-label, randomised, haloperidol-controlled study to evaluate seroquel as mono-therapy in the treatment of agitated symptoms in the patients with acute episode of schizophrenia. http://www clinicaltrials gov. 2010.
509. Silveira da Mota Neto J, Soares B, Silva de Lima M. Amisulpride for schizophrenia [systematic review]. Cochrane Database Syst Rev 2002;2009(1)
510. Sim K, Su A, Leong JY, et al. High dose antipsychotic use in schizophrenia: findings of the REAP (research on east Asia psychotropic prescriptions) study. Pharmacopsychiatry 2004;37(4):175-9.
511. Singh OP, Chakraborty I. A comparative study of oxidative stress and interrelationship of important antioxidants in haloperidol and olanzapine treated patients suffering from schizophrenia. Indian J Pscychiatry 2008;(3):171-6. PMID:19742187
512. Siu C. Missing data and dropouts in a long-term, double-blind schizophrenia study comparing ziprasidone and haloperidol. Int J Neuropsychopharmacol 2008;(Suppl 1):161.
513. Skelton JA, Pepe MM, Pineo TS. How much better is clozapine? A meta-analytic review and critical appraisal. Exp Clin Psychopharmacol 1995;3(3):270-9.
514. Smelson DA, Ziedonis D. A double blind study comparing olanzapine to haloperidol for reducing cue-elicited craving in individuals with schizophrenia and cocaine dependence. Schizophr Res 2003;60(Suppl 1):S303.
515. Smith M, Hopkins D, Peveler RC, et al. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2008;192(6):406-11. PMID:18515889
516. Soares B, Silva de Lima M. Penfluridol for schizophrenia [systematic review]. Cochrane Database Syst Rev 2006;2010(5)
517. Soares-Weiser K, Bravo VY, Beynon S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007;11(39):iii-iiv. PMID:17903393
518. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia [systematic review]. Cochrane Database Syst Rev 2006;2009(1) PMID:17903393
519. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008;61(5):455-63. PMID:18394538
520. Song F. Risperidone in the treatment of schizophrenia: a meta-analysis of randomized controlled trials. J Psychopharmacol 1997;11(1):65-71. PMID:9097896
521. Soumerai SB, Law MR, Rosenheck. Cost-effectiveness of schizophrenia pharmacotherapy. Am J Psychiatry 2007;(4):678-80. PMID:17403984
522. Soyka M, Dittert S, Schafer M, et al. Psychomotor performance under neuroleptic treatment in schizophrenia: a comparative study of haloperidol and risperidone. Z Neuropsychologie 2001;12(1):49-53.

523. Soyka M, Winter C, Kagerer S, et al. Effects of haloperidol and risperidone on psychomotor performance relevant to driving ability in schizophrenic patients compared to healthy controls. J Psychiatr Res 2005;39(1):101-8. PMID:15504428
524. Spannheimer A, Reitberger U, Clouth J, et al. Length of hospital stay and associated costs for olanzapine vs. haloperidol in the treatment of schizophrenia relapse in Germany. Eur J Health Econ 2003;4(2):85-9. PMID:15609173
525. Spivak M, Adams B, Crockford D. Atypical neuroleptic malignant syndrome with clozapine and subsequent haloperidol treatment. Can J Psychiatry 2003;48(1):66. PMID:12635570
526. Sprague DA, Loewen PS, Raymond CB. Selection of atypical antipsychotics for the management of schizophrenia. Ann Pharmacother 2004;38(2):313-9. PMID:14742771
527. Srisurapanont M, Disayavanish C, Taimkaew K. Quetiapine for schizophrenia. Cochrane Database Syst Rev 2004;2004(2) PMID:15106155
528. Stahl S, Kainer J, Hochfeld M, Baroldi P. The metabolic profile of iloperidone: summary of phase ii and iii schizophrenia trials. 2010. October 17-20, 2010; Austin, TX. American College of Clinical Pharmacy.
529. Stahl SM, Malla A, Newcomer JW, et al. Symptomatic and functional recovery index for negative symptoms in a 40-week randomized, double-blind study of ziprasidone versus haloperidol followed by a 3-yaer double-blind extension trial. Schizophr Res 2010;117(2-3):502.
530. Stip E, Tourjman V. Aripiprazole in schizophrenia and schizoaffective disorder: a review. Clin Ther 2010;32(Suppl 1):S3-S20. PMID:20152550
531. Stock E A. Long-term effects of aripiprazole and haloperidol on affective symptoms of schizophrenia. Schizophr Res 2004;(1):158-9.
532. Suh GH, Greenspan AJ, Choi SK. Comparative efficacy of risperidone versus haloperidol on behavioural and psychological symptoms of dementia. Int J Geriatr Psychiatry 2007;22(5):494-5.
533. Sundararajan V, Jainer AK. A mood stabilizer with risperidone or haloperidol for mania. Am J Psychiatry 2004;161(11):2139-40. PMID:15514433
534. Suttajit S, Srisurapanont M, Maneeton B, et al. Quetiapine versus typical antipsychotic medications for schizophrenia [protocol]. Cochrane Database Syst Rev 2009;2009(1)
535. Suzana STTG, Olivera ZOZ, Gordana NGN, et al. Adjunctive mood stabilising treatment: the effects on hostility and impulsivity among patients with schizophrenia. Eur Neuropsychopharmacol 2009;S532.
536. Svestka J. Double-blind clinical comparison of riperidon and haloperidol in acute schizophrenic and schizoaffective psychoses. Act Nerv Super (Praha) 1990;(3):237-8.
537. Swift RH, Harrigan EP, van Kammen DP. A comparison of fixed-dose, intramuscular (IM) ziprasidone with flexible-dose, IM haloperidol. 151st American Psychiatric Association Meeting 1998.
538. Swift RH, Harrigan EP, van Kammen DP. A comparison of intramuscular ziprasidone with im haloperidol conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe, New Mexico, USA 1999;17-21(298):1999.
539. Szafranski T. Subjective experiences of schizophrenic patients on atypical antipsychotic olanzapine and typical antipsychotic perphenazine. Eur Neuropsychopharmacol 1999.
540. Talbott S B. Akathisia in schizophrenia patients treated with aripiprazole, haloperidol, or olanzapine-analyses of the first 12 weeks of three double-blind, long-term trials. Proceedings of the 11th International Congress on Schizophrenia Research 2007;Apr.
541. Tamura RN, Tollefson GD, Dellva MA, et al. What is the differential risk of tardive dyskinesia with the atypical antipsychotic olanzapine? Schizophrenia Research (9th Biennial Winter Workshop on Schizophrenia) 1998;(176)
542. Tandon R, Belmaker RH, Gattaz WF, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophrenia Research 2008;100(1-3):20-38.
543. Tandon R, Fleischhacker WW. Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. Schizophr Res 2005;79(2-3):145-55. PMID:16139989
544. Taneli B. Comparison of efficacy and tolerability of quetiapine and haloperidol in acute exacerbation of chronic or subchronic schizophrenia. Eur Neuropsychopharmacol 2003;(4):S287.
545. Tapp A. Double-blind comparison of quetiapine and haloperidol on cognitive functioning in patients with schizophrenia. Schizophr Bull 2005;31(2):379.
546. Taylor D. Haloperidol, olanzapine and risperidone reduce treatment failure compared to aripiprazole, quetiapine and ziprasidone in acute schizophrenia. Evid Based Ment Health 2007;(3):76. PMID:17652558
547. Thornton AE, Van Snellenberg JX, Sepehry AA, et al. The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review. J Psychopharmacol 2006;20(3):335-46. PMID:16174678
548. Tilden D, Aristides M, Meddis D, et al. An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. Clin Ther 2002;24(10):1648-67. PMID:12462294
549. Timdahl K, Carlsson A, Stening G. An analysis of safety and tolerability data from controlled, comparative studies of quetiapine in patients with schizophrenia, focusing on extrapyramidal symptoms. Hum Psychopharmacol 2007;22(5):315-25. PMID:17542047
550. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. Bipolar Disord 2000;2(3:Pt 2):-8. PMID:11249804

551. Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. Bipolar Disord 2009;11(Suppl 54) PMID:19538685
552. Tohen M. Olanzapine versus haloperidol in the treatment of schizoaffective bipolar patients. Proceedings of the 150th Annual Meeting of the American Psychiatric Association; 1997;1997-22.
553. Tohen M. Olanzapine versus haloperidol in the treatment of schizoaffective bipolar patients. 150th Annual Meeting of the American Psychiatric Association 1997.
554. Tohen MF, Zhang F, Feldman PD, et al. Olanzapine versus haloperidol treatment of acute mania. Ann Meet Am Psychiatr Assoc 2001.
555. Tohen MF, Zhang F. Olanzapine versus haloperidol in schizoaffective bipolar disorder: a repeated-measures analysis. Proceedings of the 152nd Annual Meeting of the American Psychiatric Association 1999;20.
556. Tohen MF. Olanzapine versus haloperidol treatment of acute mania. 155th Annual Meeting of the American Psychiatric Association; 2002.
557. Tollefson G. The course of primary and secondary negative symptoms in a placebo- and comparator-controlled trial of the typical antipsychotic olanzapine. 9th European College of Neuropsychopharmacology Congress 1996.
558. Tollefson GD, Beasley CM, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. The American Journal of Psychiatry 1997;(9):1248-54. PMID:9286184
559. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol: results of the multi-centre international trial conference proceeding. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia 1996;(131)
560. Tollefson GD, Lu Y. A blinded trial on the course and relationship of depressive symptoms in schizophrenia conference abstract. 150th Annual Meeting of the American Psychiatric Association 1997.
561. Tollefson GD, Sanger TM, Beasley CM. The course of primary and secondary negative symptoms in a controlled trial with olanzapine. Eur Neuropsychopharmacol 2006;6(3):58.
562. Tollefson GD. The value of atypical antipsychotic medications conference abstract. 150th Annual Meeting of the American Psychiatric Association 1997.
563. Tran P. Acute and long-term results of the North American double-blind olanzapine trial. Eur Neuropsychopharmacol 1995;5(Supplement 1):347-8.
564. Tran P. Olanzapine in the treatment of schizoaffective disorder. Schizophrenia Research (9th Biennial Winter Workshop on Schizophrenia 1998.
565. Tran P. Olanzapine versus haloperidol: acute results of the multi-center international trial. XXth Collegium Internationale Neuro-psychopharmacologicum 2006.
566. Tran P. Olanzapine versus haloperidol: results of the international trial. 9th European College of Neuropsychopharmacology Congress 1996.
567. Tran PV, Beasley CM, Tollefson GD, et al. Clinical experience with olanzapine in patients of African, Asian, and Hispanic descent. Meeting of the American Psychiatric Association Washington, DC, USA 1999.
568. Tran PV, Beasley CM, Tollefson GD, et al. Olanzapine: a promising "Atypical" antipsychotic agent conference abstract. Schizophrenia Research (The Vth International Congress on Schizophrenia Research), Wormsprings, VA USA 1995;169.
569. Tran PV, Creanga D. Clinical experience with olanzapine in ethnic subgroups. NCDEU Boca Raton, FL, USA 1999.
570. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997;58(5):205-11. PMID:9184614
571. Tran PV, Dellva MA, Tollefson GD, et al. Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. Br J Psychiatry 1998;172:499-505. PMID:9828990
572. Tran PV, Jakovljevic M. Olanzapine versus fluphenazine: treatment of acute schizophrenic symptomatology and anxiety. Biol Psychiatry 1998;43:109S.
573. Tran PV, Tollefson GD, Crawford AM, et al. Olanzapine versus fluphenazine in schizophrenia. Proceedings of the 151st Annual Meeting of the American Psychiatric Association; 1998.
574. Tran PV, Zhang F. Efficacy and safety study comparing olanzapine versus haloperidol in the treatment of chinese patients with schizophrenia in taiwan and hong. 152nd Annual Meeting of the American Psychiatric Association 1999.
575. Tulloch KJ, Zed PJ. Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother 2004;38(12):2128-35. PMID:15522977
576. Tunis SL, Johnstone BM, Gibson PJ, et al. Changes in perceived health and functioning as a cost-effectiveness measure for olanzapine versus haloperidol treatment of schizophrenia. J Clin Psychiatry 1999;60(Suppl 45) PMID:10507279
577. Tys SM, Vlokh IY. Influence of risperidone very small doses on the negtive symptoms in schizophrenia conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe, New Mexico, USA 1999;17-21:300.
578. Umbricht D, Kane JM. Risperidone: efficacy and safety. Schizophr Bull 1995;21(4):593-606. PMID:8749887
579. Vangala S Z. Efficacy and safety study comparing olanzapine versus haloperidol in the treatment of Chinese patients with schizophrenia in Hong Kong. Proceedings of the 21st Collegium Internationale Neuro-Psychopharmacologicum Congress; 1998;-16.

580. Vargas M, Asensio N, Martn S. Effectiveness of antipsychotics in ambulatory schizophrenia: five-year retrospective cohort study. 2009 p. S78.
581. Veser FH, Zealberg J, Veser BD, et al. Oral risperidone in the management of agitated behaviours in emergency setting. 2002. Chicago, Illinois, USA, October 9-13, 2002. Annual Meeting of the American Psychiatric Association Institute on Psychiatric Services.
582. Volavka J, Citrome L. Olanzapine vs haloperidol for treatment of schizophrenia. JAMA 2004;291(9):1064-6.
583. Volavka J, Czobor P, Citrome L, et al. Efficacy of aripiprazole against hostility in schizophrenia and schizoaffective disorder: data from 5 double-blind studies. J Clin Psychiatry 2005;66(11):1362-6. PMID:16420071
584. Volavka J, Nolan KA, Kline L, et al. Efficacy of clozapine, olanzapine, risperidone, and haloperidol in schizophrenia and schizoaffective disorder assessed with nurses observation scale for inpatient evaluation. Schizophr Res 2005;76(1):127-9. PMID:15927808
585. Volavka J. Clozapine, olanzapine, risperidone, and haloperidol in refractory schizophrenia. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology 2000;14.
586. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 1999;156(7):990-9. PMID:10401441
587. Wahlbeck K, Tuunainen A, Gilbody S, et al. Influence of methodology on outcomes of randomised clozapine trials. Pharmacopsychiatry 2000;33(2):54-9. PMID:10761820
588. Wang CH, Zhao Z, Li Y, et al. Evaluation of proximal therapeutic effect and distal social function restoration of olanzapine on schizophrenia patients. Chin J Clin Rehabil 2002;6(17):2664-5.
589. Weiden PJ, Cutler AJ, Polymeropoulos MH, et al. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol 2008;28(2:Suppl 1):-9. PMID:18334908
590. Weiser M, Shneider-Beeri M, Nakash N, et al. Improvement in cognition associated with novel antipsychotic drugs: a direct drug effect or reduction of EPS? Schizophr Res 2000;46(2-3):81-9. PMID:11120419
591. Williams LM, Loughland CM, Green MJ, et al. Emotion perception in schizophrenia: an eye movement study comparing the effectiveness of risperidone vs. haloperidol. Psychiatry Res 2003;120(1):13-27. PMID:14500110
592. Windhaber J, Urbanits S, Grisold W. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. Neurology 2000;54(7):1543-4. PMID:10751282
593. Winlow W, Profit L, Chrisp P. Aripiprazole: the evidence of its therapeutic impact in schizophrenia. Core Evid 2006;1(4):251-64.
594. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002;63(10):856-65. PMID:12416594
595. Wirshing DA, Marder SR, Wirshing WC. Subjective response to atypical antipsychotic medications conference abstract. Schizophrenia Research (Abstracts of The VIIth International Congress on Schizophrenia Research), Santa Fe New Mexico USA 1999;17-21(302)
596. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60(6):358-63. PMID:10401912
597. Wirshing WC, Ames D. Risperidone versus haloperidol in treatment-refractory schizophrenia: preliminary results. Psychopharmacol Bull 1995;(3):633.
598. Wirshing WC, Ames D. Risperidone vs haloperidol in treatment resistant schizophrenia: preliminary results conference proceeding. Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia) 1996;18(2-3):130.
599. Wolwer W. Effects of risperidone vs. haloperidol on neurocognition in first-episode schizophrenia: results from a rct. Int J Neuropsychopharmacol 2008;(Suppl 1):159.
600. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64(6):663-7. PMID:12823080
601. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. Schizophr Res 2007;89(1-3):211-24. PMID:17059880
602. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol 2005;8(3):457-72. PMID:15784157
603. Wright P. A double-blind dose response study comparing intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. Schizophr Res 2001;49(2 Suppl 1):250-1.
604. Wright P. A double-blind study of intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. Int J Neuropsychopharmacol 2000;(Suppl 1):S139.
605. Yang YK, Tarn YH, Wang TY, et al. Pharmacoeconomic evaluation of schizophrenia in Taiwan: model comparison of long-acting risperidone versus olanzapine versus depot haloperidol based on estimated costs. Psychiatry Clin Neurosci 2005;59(4):385-94. PMID:16048443
606. Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. Emerg Med J 2003;20(4):339-46. PMID:12835344
607. Yocca F. Intramuscular aripiprazole in acute schizophrenia: a pivotal phase-three study. 158th Annual Meeting of the American Psychiatric Association; 2005.

608. Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. Clin Ther 2010;32(3):403-25.
609. Zhang B. A 4-week, randomized, rater-blinded, parallel-group, haloperidol-controlled study to evaluate the efficacy of quetiapine fumarate in improving sleep quality in the patients with schizophrenia. Int J Neuropsychopharmacol 2010;113-4.
610. Zhang F. Olanzapine versus haloperidol: assessment of cognitive function in patients with schizoaffective disorder, bipolar type. Eur Neuropsychopharmacol 1999;9(Suppl 5):247.
611. Zhang XY, Zhou DF, Shen YC. Effects of risperidone and haloperidol on paroxetine-evoke neuroendocreine responses in schizophrenia. Schizophrenia Research (Xth Biennial Winter Workshop on Schizophrenia) 2000;11.
612. Zinner HJ., Fuger J. Changes of positive and negative syndromes: a double-blind clinical trial with risperidone versus haloperidol in chronic schizophrenia. Pharmacopsychiatry 1992;25:118.

Non-English Language Publication

1. Adrianzen C. Olanzapine versus haloperidol: effectiveness in functionality and health state in a sample of Venezuelan patients with schizophrenia. Vertex 2008;(81):254-60. PMID:19835025
2. Ai L. A comparative study of efficacy and safety of seroquel versus chlorpromazine in the treatment of schizophrenia. Heilongjiang Med J 2007;(4):285.
3. An QH, Hu KY, Meng XL. A comparison of intelligence disorders and memory disorders in the first-onset schizophrenia treated with quetiapine and chlorpromazine. Chin J Behav Med Sci 2005;(1):62-3.
4. Ao X. Comparative study between aripiprazole and chlorpromazine in the treatment of female patients with schizophrenia. Med J Chin Civil Admin 2006;(17):719-20.
5. Bai Y. A random chlorpromazine-controlled study of the effects of quetiapine on cognition in schizophrenia. Shanghai Arch Psychiatry 2005;(3):151-4.
6. Bian QT, Xie GR. A comparative study of quality of life in schizophrenia treated with chlorpromazine, clozapine or risperidone. Chin J Clin Psychol 2003;(2):125-7.
7. Blaeser-Kiel G. Schizophrenes negativsyndrom risperidone erfolgreich. Neurologie Psychiatrie 1994;(11):614-5.
8. Bouchard RH. Longitudinal comparative study of risperidone vs classical neuroleptics in the treatment of schizophrenia: 24 months of observation. L'Encephale 2002;2 PMID:12587355
9. Cao D. Characteristics of the sexual disturbance caused by chlorpromazine, risperidone, quetiapine and olanzapine and their associations with the changes of blood glucose and blood lipids in male patients with schizophrenia. Chin J Clin Rehabil 2005;(36):63-8.
10. Cao D. Comparison of the effects of chlorpromazine, risperidone and quetiapine on hypothalamic-pituitary-gonodal axis and sexual function in male patients with schizophrenia. Chin J Rehabil 2005;(20):148-51.
11. Cao KS, Yao J. Safety and efficacy of ziprasidone and haloperidol in patients with schizophrenia. Chin J New Drug Clin Remed 2006;(6):431-4.
12. Ceskova E, Svestka. Efficacy and tolerance of risperidone in various doses (report of a study). Ceska Slov Psychiatr 1996;Purkyne.(1):50-6. PMID:8768938
13. Chang FW, Wang CH, Zhao. Clinical effects of olanzapine vs chlorpromazine in treating positive symptoms of schizophrenia. Chin J New Drug Clin Remed 2003;(6):357-9.
14. Chang SH. Comparative study of loxapine and risperidone in the treatment of schizophrenia. Med J Chin People Health 2006;(12):1020-1.
15. Chen Q. A comparative study of the effects of clozapine, risperidone and chlorpromazine on sugar metabolism in schizophrenic treatment. Chin J Clin Health Psychol 2007;(4):382-3.
16. Cheng XF. Control observation of quetiapine vs chlorpromazine in schizophrenia. J Clin Psychosom Dis 2003;(2):78-80.
17. Chung YC, Park KH, Kim DJ, et al. Prolactin response to the administration of risperidone and haloperidol in patients with schizophrenia and other psychotic disorders. Korean J Psychopharmacol 2000;(4):343-9.
18. Cui B. A comparative study of the effects of risperidone, chlorpromazine and clozapine to patients with schizophrenia by the electrocardiograms. Tianjin Pharm 2002;-55.
19. Cui LI, Tian G. Serum levels of prolactin and growth hormone and effect of pharmacotherapy on schizophrenia: a comparative study of risperidone and chlorpromazine. Chin Ment Health J 1999;(6):368-70.
20. Dongfeng Z. Effects of risperidone and haloperidol on paroxetine-evoked neuroendocrine responses in schizophrenia. Chin J Psychiatry 1999;(2):84-7.
21. Du BG, Fang RL. Control studies on curative effects of loxapine succinate and risperidone in schizophrenics. J Clin Psychosom Dis 2003;(1):16-9.
22. Du QX, Yu CF, Zhong. A clinical comparative analysis of quetiapine and chlorpromazine in treatment of schizophrenia. Med J Chin People Health 2004;(7):398-9.
23. Fan J. Effect of risperidone and chlorpromazine on cognition in first-episode schizophrenia. Chin J Clin Health Psychol 2006;(4):422-4.

24. Feng CX, Huang SX, Yang HZ. A comparative trial on the efficacy of risperidone vs chlorpromazine in treatment-resistant schizophrenia. Shandong Arch Psychiatry 2001;(2):95-6.
25. Gaszner P. Clinical observations with aripiprazole in schizophrenia. Neuropsychopharmacol Hung 2006;(1):29-32. PMID:16841563
26. Ge Q. A comparative study of risperidone combining clonazepam and haloperidol in the treatment of patients with schizophrenia. Shandong Arch Psychiatry 2004;(3):134-6.
27. Guo BY, Wang YB. Control studies on efficacy of quetiapine vs chlorpromazine in first- episode schizophrenics. J Clin Psychosom Dis 2003;(2):75-7.
28. Guo J. Effect of quetiapine and chlorpromazine on cognitive function in first-episode schizophrenic. Chin J Clin Health Psychol 2007;(7):583-4.
29. He M. A controlled comparative study on risperidone and chlorpromazine in treatment of schizophrenia. Chin New Drugs J 1999;(3):185-7.
30. He YD, Zhao CM, Shao AL, et al. A comparative study of quetiapine and chlorpromazine in the treatment of patients with schizophrenia. Herald Med 2003;(10):680-2.
31. Hou YZ, Guo JH, Zhou. The double-blind study of risperidone and haloperidal in the treatmentof schizophrenia. Shanghai Psychol Med 2001;(3):149-51.
32. Huang J. Comparison of compliance and effectiveness of quetiapine and haloperidol in the treatment of schizophrenia. Int Med Health Guid News 2007;(16):96-9.
33. Huang SX, Feng CX, Chen JY, et al. Risperidone vs chlorpromazine in treating schizophrenia: a randomized double-blind study. Chin J New Drug Clin Remed 2000;(5):396-8.
34. Jager M. Pharmacological acute treatment in first episode schizophrenic disorders. Nervenheilkunde 2006;(1-2):32-6.
35. Jarema M. Safety and efficacy of olanzapine versus perphenazine in patients with schizophrenia: results of multicenter, 18-week, double-blind clinical trial. Psychiatr Pol 2003;(4):641-55. PMID:14560493
36. Ji J. Comparative study between the quality of life and its curative effect in schizophrenic patients treated with quetiapine or chlorpromazine. Sichuan Ment Health 2004;(2):73-5.
37. Jiang KD, Bai YL, Peng DH, et al. A random and controlled study of quetiapine and chlorpromazine in patients with schizophrenia. Linchuang Jingshen Yixue Zazhi 2006;(6):352-3.
38. Jin S L. Seroquel and chlorpromazine in treatment of schizophrenia: a random, controlled trial. China Pharm 2007;(19):56-7.
39. Ju FenYing, Zhu DongSheng, Liu Yan Lu Wei hong, et al. The randomised control trial of thioridazine and sulpiride treating schizophrenia with negative symptoms. Sichuan Ment Health 1997;10(3):171-2.
40. Kong DL, Zhang SQ, Shu MQ. Effects of quetiapine and chlorpromazine on serum prolactin of schizophrenics. J Clin Psychosom Dis 2003;(4):200-1.
41. Le PC. Economic comparison of olanzapine versus haloperidol in treatment of schizophrenia in France. L'Encephale 1999;(4):281-6. PMID:10546082
42. Leon CA, Estrada H. Efectors terapeuticos de la clozapina sobre los sintomas de psicosis. Revista Colombiana de Psiquiatria 1974;3:309-18.
43. Li C. A controlled study of olanzapine and haloperidol in the treatment of the acute phase of schizophrenia. Shanghai Arch Psychiatry 2005;(5):275-7.
44. Li LH, Fang MS, Xu XF, et al. Ziprasidone vs haloperidol in treatment of schizophrenia: a randomized, double-blind, double-dummy, multicenter, parallel control study. Chin J New Drug Clin Remed 2007;(5):335-8.
45. Li LX LC. A comparative study of loxapine succinate and risperidone in the treatment of schizophrenia. Shandong Arch Psychiatry 2005;(4):246-7.
46. Li Y, Shang J, Li C. Control study of loxapine succinate and clozapine on curative effects in treatment of schizophrenics. Heath Psychology Journal 2004;12(3):202.
47. Li Y. A comparative effects of aripiprazole and haloperidol on the cognitive dysfunction in the treatment of first episode schizophrenic patients. Sichuan Ment Health 2006;(3):150-2.
48. Li ZY HR. Comparative study between loxapine and risperidone in treatment of schizophrenia. J Clin Psychol Med 2005;(1):11-2.
49. Lin HL, Shi WH, Wang JH. Effects of aripiprazole and chlorpromazine on the cognitive function in first-episode schizophrenia patients. Chin J Behav Med Sci 2006;(5):440-2.
50. Liu BingLang, Chen YY, Yang DS. Effects of thioridazine on schizophrenics and clinical utility of plasma levels. Chin J Neurol Psychiatry 1994;27:364-7.
51. Liu BL, Chen YY, Yang DS. Effects of thioridazine on schizophrenics and clinical utility of plasma levels. Chin J Neurol Psychiatry 1994;27:364-7.
52. Liu G. A comparative study on risperidone and perphenazine in the treatment of schizophrenic patients. Shandong Arch Psychiatry 2001;(3):170-2.
53. Liu Y. A comparative study of risperdal and chlorpromazine in the treatment of the negative symptoms of schizophrenia. Herald Med 2000;(4):323-4.
54. Lopez Ibor JJ, Ayuso JL, Gutierrez. Risperidone in the treatment of chronic schizophrenia: multicenter study comparative to haloperidol. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1996;(4):165-72. PMID:8984849
55. Lu X-Q, Zhu G-L. Control studies of loxapine succinate and clozapine in treatment of schizophrenia. J Clin Psychosom Dis 2003;9(3):157-8.
56. Lu ZD, Cao YN, Wang. A comparative study of aripiprazole and chlorpromazine in the treatment of schizophrenia. Shandong Jingshen Yixue 2006;(2):90-2.

57. Luo X. Comparison of effects and factors between risperidone and chlorpromazine on schizophrenia. Chin J New Drug Clin Remed 2001;-266.
58. Ma ZH, Liu AY, Zhou CM, et al. A comparative study of risperidone and chlorpromazine in the treatment of schizophrenia. Med J Chin People Health 2004;(4):202-4.
59. Ma ZW, Li MX, Shi YZ, et al. Quetiapine (35 patients) vs chlorpromazine (34 patients) in treatment of schizophrenia. Chin J New Drug Clin Remed 2004;(5):273-5.
60. Mei AC. Comparison of efficacy and safety of quetiapine and chlorpromazine in the treatment of schizophrenia. Med J Chin People Health 2007;(17):723-4.
61. Murasaki M. Clinical evaluation of quetiapine fumarate on schizophrenia: comparative double-blind study with haloperidol. Seishin Igaku 2001;(1):127-55.
62. Murasaki M. Efficacy of a new antipsychotic, risperidone, on schizophrenia: a comparative double blind study with haloperidol. Rinsho Hyoka 1993;(2):221-59.
63. Peng YH, Zhu ZX, Yang YX. Effect on prolactin of quetiapine and chlorpromazine in male schizophrenia. Med J Chin Civil Admin 2006;(9):760-1.
64. Peng ZG, Zhou JX, Kuang WH, et al. A randomized double - blind controlled study on the efficacy of quetiapine and chlorpromazine in treatment of schizophrenia. West China J Pharm Sci 2006;(6):606-8.
65. Qin Y. A comparative trial of olanzapine versus haloperidol in the treatment of schizophrenia. Hebei Med 2006;(10):1011-3.
66. Qiu Y. A comparative study between quetiapine and haloperidol on the life quality of the patients with schizophrenia. Shandong Arch Psychiatry 2003;(3):138-40.
67. Ren QT YJL. Effect of haloperidol and risperidone on the life quality of the patients with schizophrenia. Chin J Clin Psychol 2002;(2):150-1.
68. Sheng Y. A comparison study of the blood sugar in the treatment of schizophrenic patients with risperidone, clozapine and chlorpromazine. Qilu Journal of Medicall Aboratory Sciences 2003;(1):11-2.
69. Tian H. Comparative study on the effect of seroquel and chlorpromazine on schizophrenia. China Pharmacy 2006;(9):682-3.
70. Tu ZM, Deng XP, Ca DM. Comparative study between aripiprazole and chlorpromazine in treatment of schizophrenia. Med J Chin People Health 2007;(17):715-6.
71. Wang C. A clinical study of risperidone, clozapine and chlorpromazine in patients with first-episode schizophrenia. J Clin Psychosom Dis 2006;(1):7-9.
72. Wang C. Comparative study on the life quality of first-episode schizophrenics treated with risperidone, clozapine and chlorpromazine. J Clin Psychosom Dis 2006;(2):87-9.
73. Wang G-P. A comparative study between aripiprazole and chlorpromazine in the treatment of schizophrenia. Shandong Arch Psychiatry 2005;18(4):250-1.
74. Wang H. Safety and efficacy of quetiapine and haloperidol in the treatment of schizophrenia with excitement and agitation. Shanghai Arch Psychiatry 2005;(5):271-4.
75. Wang LG, Liu Y. A comparative trial of the efficacy on olanzapine and chlorpromazine in treatment-resistant schizophrenia. Heath Psychology Journal 2004;(3):203-4.
76. Wang LG, Wang DM, Su. A comparative study of aripiprazole and haloperidol in the treatment of patient with treatment-resistant schizophrenia. Nerv Dis Ment Hygjene 2006;(1):38-9.
77. Wang Q. Controlled study of risperidone and chlorpromazine in the treatment of schizophrenia. Health Psychol J 2002;(3):226-8.
78. Wang RC, Li LH, Zhao YC. Ziprasidone made in China and haloperidol in treating acute onset of schizophrenia: a randomized, single blinded, double modelling, parallel control study. Chin J Clin Rehabil 2005;(44):83-5.
79. Wang X. Effect of chlorpromazine and risperidone on coginition function of the patients with first episode schizophrenia. Heath Psychology Journal 2005;(5):342-4.
80. Wang. Control study of loxapine and quetiapine treating first onset schizophrenia. Chin J Behav Med Sci 2005;14(8):752.
81. Wu S X. A comparative trial on the efficacy of risperidone vs chlorpromazine in chronic schizophrenia. Health Psychol J 2002;(5):364-5.
82. Wu Y. A comparative study of risperidone and chlorpromazine on quality of life in patients with schizophrenica. Shandong Arch Psychiatry 2004;(3):137-40.
83. Xia SY HP. A treatment study of schizophrenia with aripiprazole and chlorpromazine. Pract Clin Med 2005;(10):33-4.
84. Xia SY WC. A comparison between the therapeutic effectiveness and safeness of aripiprazole and chlorpromazine in the treatment of first-episode schizophrenia. Herald Med 2007;(6):619-20.
85. Xu WR, Bao-Long Z, Qui C. A double-blind study of clozapine and chlorpromazine treatment in the schizophrenics. Chin J Nerv Ment Dis 1985;11:222-4.
86. Yang B. Effects of clozapine, risperidone and haloperidol on plasma leptin in first-episode schizophrenic patients. J Fourth Mil Med Univ, 2004;(14):1323-5.
87. Yu J. A comparison of cognitive function in schizophrenia treated with risperidone and chlorpromazine. J Clin Psychol Med 2001;(5):265-6.
88. Zhang F. Olanzapine versus haloperidol in schizoaffective disorder, bipolar type: a repeated measures analysis conference abstract. Schizophr Res 1999;17-21(303)

89. Zhang HY, Wang X. A comparison study on efficacy and safety of quetiapine and chlorpromazine in the treatment of schizophrenia. Chin J Clin Pharmacol 2003;(3):163-6.
90. Zhang S L. A double-blind study of domestic quetiapine and chlorpromazine in the treatment of schizophrenia. Shandong Arch Psychiatry 2002;(3):149-51.
91. Zhang WMJG, Xu FL. Comparison study on treatment of primary schizophrenia with quetiapine and chlorpromazine. Heilongjiang Med J 2006;(2):81-2.
92. Zhang X. The effect of risperidone and haloperidol treatment on plasma interleukin 2, 6, 8 in inpatients with schizophrenia and their relationship to outcome. Chin J Nerv Ment Dis 2000;(4):222-4.
93. Zhao JP, Chen JD, Chen YG, et al. A double-blind and double-dummy comparative study of quetiapine and chlorpromazine in the treatment of schizophrenia. Chin New Drugs J 2002;(2):149-51.
94. Zhao Z. A comparative study on olanzapine and chlorpromazine in the treatment of schizophrenia. Chin J Clin Health Psychol 2006;(1):41-2.
95. Zheng X. A double blind comparing study between the effects of haloperidol and olanzapine on the quality of life of the patients with schizophrenia. J Jining Med Coll 2004;(3):20-2.
96. Zheng ZB, Ma ZF, Zhang LL. A comparative study of the effects of olanzapine and perphenazine on schizophrenia and the patients' quality of life. J Linyi Med Coll 2004;(4):273-5.
97. Zhou J. Comparison between quetiapine and chlorpromazine in cognitive function of schizophrenic patients. Chin Ment Health J 2003;(10):699-1.
98. Zhou M. Double-blind comparison between risperidone and haloperidol in the treatment of schizophrenic patients. Chin J Clin Pharmacol 2002;(5):341-4.
99. Zhou SB, Sun XD, Li YM. A comparative study on quetiapine and chlorpromazine in the treatment of schizophrenia. Med J Chin People Health 2004;(11):657-9.
100. Zou JH, Zhou Y. A clinical analysis between quetiapine and haloperidol in the treatment of schizophrenia. Med J Chin People Health 2007;19(11):434-7.

Population and Intervention Characteristics

1. Advokat C, Hill BD, Comaty JE. 'Real world' comparison of first- and second-generation antipsychotics in regard to length of inpatient hospitalization and number of re-hospitalizations. Psychiatr Q 2008;79(1):55-64. PMID:18060498
2. Akkaya C, Sarandol A, Cangur S, et al. Retrospective database analysis on the effectiveness of typical and atypical antipsychotic drugs in an outpatient clinic setting. Hum Psychopharmacol Clin Exp 2007;22(8):515-28. PMID:17868197
3. Altamura AC, Velona I, Curreli R. Olanzapine in the traetment of paranoid schizophrenia. Eur Neuropsychopharmacol 2002;9(Suppl5):S297.
4. Alvarez E, Bobes J, Gomez JC, et al. Safety of olanzapine versus conventional antipsychotics in the treatment of patients with acute schizophrenia: a naturalistic study. Eur Neuropsychopharmacol 2003;13(1):39-48. PMID:12480121
5. Appelberg B, Tuisku K, Joffe G. Is it worth while changing clinically stable schizophrenic out-patients with mild to moderate residual symptoms and/or side effects from conventional to atypical antipsychotics?: a prospective, randomised study with olanzapine. Eur Psychiatry 2004;19(8):516-8. PMID:15589715
6. Archibald DG, Manos G, Tourkodimitris S. Reduction in negative symptoms of schizophrenia during long term therapy with aripiprazole. Schizophr Res 2003;60(Suppl1):271.
7. Ascher-Svanum H, Stensland MD, Kinon BJ, et al. Weight gain as a prognostic indicator of therapeutic improvement during acute treatment of schizophrenia with placebo or active antipsychotic. J Psychopharmacol 2005;19(6:Suppl):-7. PMID:16280344
8. Barbui C, Accordini S, Nos+¨ M, et al. Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia in routine clinical care: A randomized, controlled trial. J Clin Psychopharmacol 2011;31(3):266-73. PMID:21508849
9. Bisconer SW, Harte BM. Patterns and prevalence of metabolic syndrome among psychiatric inpatients receiving antipsychotic medications: Implications for the practicing psychologist. Prof Psychol Res Pract 2010;41(3):244-52.
10. Bobes J, Gibert J, Ciudad A, et al. Safety and effectiveness of olanzapine versus conventional antipsychotics in the acute treatment of first-episode schizophrenic inpatients. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(3):473-81. PMID:12691783
11. Bobo WV, Jayathilake K, Lee MA, et al. Changes in weight and body mass index during treatment with melperone, clozapine and typical neuroleptics. Psychiatry Res 2010;176(2-3):114-9. PMID:20199813
12. Bond GR, Kim HW, Meyer PS, et al. Response to vocational rehabilitation during treatment with first- or second-generation antipsychotics. Psychiatr Serv 2004;55(1):59-66. PMID:14699202
13. Bouchard RH, Merette C, Pourcher E, et al. Longitudinal comparative study of risperidone and conventional neuroleptics for treating patients with schizophrenia. J Clin Psychopharmacol 2000;20(3):295-304. PMID:10831015
14. Brar JS, Parepally H, Chalasani L, et al. The impact of olanzapine on tardive dyskinetic symptoms in a state hospital population. Ann Clin Psychiatry 2008;20(3):139-44. PMID:18633740

15. Brewer WJ, Yucel M, Harrison BJ, et al. Increased prefrontal cerebral blood flow in first-episode schizophrenia following treatment: longitudinal positron emission tomography study. Aust NZ J Psychiatry 2007;41(2):129-35. PMID:17464690
16. Broich K, Grunwald F, Kasper S, et al. D2-dopamine receptor occupancy measured by IBZM-spect in relation to extrapyramidal side effects. Pharmacopsychiatry 1998;31(5):159-62. PMID:9832346
17. Brugnoli R, Novick D, Frediani S, et al. Efficacy of antipsychotic treatment in schizophrenia: Results after 24 months in Italian patients in the Schizophrenia Outpatient Health Outcomes (SOHO) study. Ital J Psychopathol 2007;13(3):330-40.
18. Carlson C, Hornbuckle K, DeLisle F, et al. Diabetes mellitus and antipsychotic treatment in the United Kingdom. Eur Neuropsychopharmacol 2006;16(5):366-75. PMID:16356695
19. Carrasco JL, Gutierrez M, Gomez JC, et al. Treatment of severely psychotic inpatients with schizophrenia: olanzapine versus other antipsychotic drugs. Int Clin Psychopharmacol 2002;17(6):287-95. PMID:12409682
20. Carson WH, Pigott TA, Saha AR. Aripirazole versus placebo in the treatment of chronic schizophrenia [abstract]. 2002 p. S187.
21. Castle DJ, Udristoiu T, Kim CY, et al. Intramuscular olanzapine versus short-acting typical intramuscular antipsychotics: comparison of real-life effectiveness in the treatment of agitation. World J Biol Psychiatry 2009;10(1):43-53. PMID:19137460
22. Ciranni MA, Kearney TE, Olson KR. Comparing acute toxicity of first- and second-generation antipsychotic drugs: a 10-year, retrospective cohort study. J Clin Psychiatry 2009;70(1):122-9. PMID:19192473
23. Coley KC, Carter CS, DaPos SV, et al. Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol. J Clin Psychiatry 1999;60(12):850-6. PMID:10665632
24. Cortese L, Caligiuri MP, Williams R, et al. Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. J Clin Psychopharmacol 2008;28(1):69-73. PMID:18204344
25. Costa AMN, De Lima MS, Faria M, et al. A naturalistic, 9-month follow-up, comparing olanzapine and conventional antipsychotics on sexual function and hormonal profile for males with schizophrenia. J Psychopharmacol 2007;21(2):165-70. PMID:17329296
26. Covell NH, Weissman EM, Essock SM. Weight gain with clozapine compared to first generation antipsychotic medications. Schizophr Bull 2004;30(2):229-40. PMID:15279042
27. Currier GW, Chou JC, Feifel D, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. J Clin Psychiatry 2004;65(3):386-94. PMID:15096079
28. Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. J Clin Psychiatry 2001;62(3):153-7. PMID:11305699
29. Czekalla J, Dittmann RW, Holstein W, et al. Olanzapine (Zyprexa) treatment in patients pre-treated with other antipsychotics: pharmacovigilance data from a large drug utilization observation (DUO) study in Germany. Germ J Psychiatry 2005;8(3):49-59.
30. Daniel DG, Saha AR, Ingenito GG. Aripiprazole, a novel antipsychotic: overview of a phase II study result. Int J Neuropsychopharmacol 2000;3(Suppl1):S157.
31. Daniel DG, Zimbroff DL, Swift RH, et al. The tolerability of intramuscular ziprasidone and haloperidol treatment and the transition to oral therapy. Int Clin Psychopharmacol 2004;19(1):9-15. PMID:15101564
32. Daniel J, Chamberlain J, Castle DJ. The pharmacological management of behavioural disturbance in psychosis: a naturalistic study. Australas Psychiatry 2007;15(5):380-4. PMID:17828634
33. Daskalakis ZJ, Christensen BK, Chen R, et al. Effect of antipsychotics on cortical inhibition using transcranial magnetic stimulation. Psychopharmacology (Berl) 2003;170(3):255-62. PMID:12904966
34. De Hert M, Schreurs V, Sweers K, et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophr Res 2008;101(1-3):295-303. PMID:18299188
35. Diaz E, Neuse E, Sullivan MC, et al. Adherence to conventional and atypical antipsychotics after hospital discharge. J Clin Psychiatry 2004;65(3):354-60. PMID:15096075
36. Diehl A, Reinhard I, Schmitt A, et al. Does the degree of smoking effect the severity of tardive dyskinesia?: a longitudinal clinical trial. Eur Psychiatry 2009;24(1):33-40. PMID:18774276
37. Dittmann RW, Geuppert MS, Diehl. Olanzapine versus flupentixol in the treatment of inpatients with schizophrenia: a randomised double-blind trial. Schizophr Res 2001;(1-2):225.
38. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002;159(1):103-8. PMID:11772697
39. Dose M, Glaser T, Weinmuller B. Treating schizophrenia patients with antipsychotics in a naturalistic setting: a retrospective chart review. Psychiatrie 2008;12(4):197-200.

40. Emsley R, Rabinowitz J, Medori R, et al. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. Schizophr Res 2007;89(1-3):129-39. PMID:17095194
41. Engelborghs S, Holmes C, McCulley M, et al. 5-HT2A receptor polymorphism may modulate antipsychotic treatment response in Alzheimer's disease. Int J Geriatr Psychiatry 2004;19(11):1108-9. PMID:15497194
42. Freeman HL. Amisulpride compared with standard neuroleptics in acute exacerbations of schizophrenia: three efficacy studies. Int Clin Psychopharmacol 1997;12(Suppl7) PMID:9218163
43. Gaertner I, Altendorf K, Batra A, et al. Relevance of liver enzyme elevations with four different neuroleptics: a retrospective review of 7,263 treatment courses. J Clin Psychopharmacol 2001;21(2):215-22. PMID:11270919
44. Garver DL, Holcomb JA, Christensen JD. Cerebral cortical gray expansion associated with two second-generation antipsychotics. Biol Psychiatry 2005;58(1):62-6. PMID:15992524
45. Gerlach J, Simmelsgaard H. Tardive dyskinesia during and following treatment with haloperidol, haloperidol + biperiden, thioridazine, and clozapine. Psychopharmacology (Berl) 1978;59(2):105-12. PMID:103110
46. Gilbody SM, Bangall AM, Duggan L. Risperidone versus other atypical antipsychotic medication for schizophrenia. The Cochrane Collaboration 2000;(3) PMID:10908551
47. Godleski LS, Goldsmith LJ, Vieweg WV, et al. Switching from depot antipsychotic drugs to olanzapine in patients with chronic schizophrenia. J Clin Psychiatry 2003;64(2):119-22. PMID:12633119
48. Guha P, Roy K, Sanyal D, et al. Olanzapine-induced obesity and diabetes in Indian patients: a prospective trial comparing olanzapine with typical antipsychotics. J Indian Med Assoc 2005;103(12):660-4. PMID:16821658
49. Haro JM, Edgell ET, Novick D, et al. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. Acta Psychiatr Scand 2005;111(3):220-31. PMID:15701107
50. Haro JM, Suarez D, Novick D, et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. Eur Neuropsychopharmacol 2007;17(4):235-44. PMID:17137759
51. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol 2004;24(1):62-9. PMID:14709949
52. Harvey PD, Endicott JM, Loebel AD. The factor structure of clinical symptoms in mixed and manic episodes prior to and after antipsychotic treatment. Bipolar Disord 2008;(8):900-6. PMID:19594505
53. Hassan M, Madhavan SS, Kalsekar ID, et al. Comparing adherence to and persistence with antipsychotic therapy among patients with bipolar disorder. Ann Pharmacother 2007;41(11):1812-8. PMID:17925501
54. Haupt DW, Fahnestock PA, Flavin KA, et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. Neuropsychopharmacology 2007;32(12):2561-9. PMID:17375138
55. Hayhurst KP, Drake RJ, Lewis SW. Patient factors associated with receipt of combination antipsychotic drug therapy in the treatment of schizophrenia. J Psychopharmacol 2010;24(1):83-9. PMID:18719041
56. Herrera JN, Sramek JJ, Costa JF, et al. High potency neuroleptics and violence in schizophrenics. J Nerv Ment Dis 1988;176(9):558-61. PMID:3418329
57. Heydebrand G, Weiser M, Rabinowitz J, et al. Correlates of cognitive deficits in first episode schizophrenia. Schizophr Res 2004;68(1):1-9. PMID:15037334
58. Hori H, Noguchi H, Hashimoto R, et al. Antipsychotic medication and cognitive function in schizophrenia. Schizophr Res 2006;86(1-3):138-46. PMID:16793238
59. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. Eur Neuropsychopharmacol 1995;5(4):437-40. PMID:8998394
60. Hummer M, Sperner-Unterweger B, Kemmler G, et al. Does eosinophilia predict clozapine induced neutropenia? Psychopharmacology (Berl) 1996;124(1-2):201-4. PMID:8935817
61. Inada T, Murasaki M. The drug induced extrapyramidal symptoms scale: differentiation of extrapyramidal symptom profile and identification of favourable extrapyramidal symptom profile of quetiapine in Japanesepatients. Eur Neuropsychopharmacol 2001;11(Suppl3):S265.
62. Jerrell JM, Ramirez PM. Changes in neuropsychological functioning following treatment with risperidone, olanzapine, and conventional antipsychotic medications. Hum Psychopharmacol Clin Exp 2008;23(7):595-604. PMID:18680213
63. Joffe G, Sintonen H, Appelberg B. Shift from first generation antipsychotics to olanzapine may improve health-related quality of life of stable but residually symptomatic schizophrenic outpatients: a prospective, randomized study. Int J Technol Assess Health Care 2008;24(4):399-402. PMID:18828933
64. Jones B, Tollefson GD. Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. Schizophr Res 1998;29:150-1.
65. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006;63(10):1079-87. PMID:17015810

66. Keck PEJr, Corya SA, Altshuler LL, et al. Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression. J Clin Psychiatry 2005;66(5):611-6. PMID:15889948
67. Kelly DL, Weiner E, Ball MP, et al. Remission in schizophrenia: the relationship to baseline symptoms and changes in symptom domains during a one-year study. J Psychopharmacol 2009;23(4):436-41. PMID:18583442
68. Kennedy E, Song F, Hunter R. Risperidone versus typical antipsychotic medication for schizophrenia. The Cochrane Collaboration 2000;(2) PMID:10796543
69. Kennedy J, Tien YY, Cohen LJ, et al. The association between class of antipsychotic and rates of hospitalization: results of a retrospective analysis of data from the 2005 Medicare current beneficiary survey. Clin Ther 2009;31(12):2931-9. PMID:20110033
70. Kim CY, Chung S, Lee JN, et al. A 12-week, naturalistic switch study of the efficacy and tolerability of aripiprazole in stable outpatients with schizophrenia or schizoaffective disorder. Int Clin Psychopharmacol 2009;24(4):181-8. PMID:19451828
71. Kinon BJ, Basson BR, Gilmore JA, et al. Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry 2000;61(11):833-40. PMID:11105736
72. Knegtering H, van den Bosch R, Castelein S, et al. Are sexual side effects of prolactin-raising antipsychotics reducible to serum prolactin? Psychoneuroendocrinology 2008;33(6):711-7. PMID:18395353
73. Kufferle B, Brucke T, Topitz-Schratzberger A, et al. Striatal dopamine-2 receptor occupancy in psychotic patients treated with risperidone. Psychiatry Res 1996;68(1):23-30. PMID:9027930
74. Kujawa M, Saha AR, Ingenito GG. Aripiprazole for long-term maintenance treatment of schizophrenia [abstract]. Int J Neuropsychopharmacol 2002;5(1):S186-S187.
75. Kurz M, Hummer M, Oberbauer H, et al. Extrapyramidal side effects of clozapine and haloperidol. Psychopharmacology (Berl) 1995;118(1):52-6. PMID:7597122
76. Lambert MT, Copeland LA, Sampson N, et al. New-onset type-2 diabetes associated with atypical antipsychotic medications. Prog Neuropsychopharmacol Biol Psychiatry 2006;30(5):919-23. PMID:16581171
77. Lauriello J, Kainer J, Hochfeld M, Torres R. Extrapyramidal symtom and akathesia profile of iloperidone in schizophrenia clinical trials. 2010. October 17-20, 2010; Austin, TX. American College of Clinical Pharmacy.
78. Lee C, Wu KH, Habil H, et al. Treatment with olanzapine, risperidone or typical antipsychotic drugs in Asian patients with schizophrenia. Aust NZ J Psychiatry 2006;40(5):437-45. PMID:16683970
79. Lee MA, Jayathilake K, Meltzer HY. A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. Schizophr Res 1999;37(1):1-11. PMID:10227103
80. Leelahanaj T, Kongsakon R, Netrakom P. A 4-week, double-blind comparison of olanzapine with haloperidol in the treatment of amphetamine psychosis. J Med Assoc Thai 2005;88(Suppl3):S43-S52. PMID:16858942
81. Letmaier M, Schreinzer D, Reinfried L, et al. Typical neuroleptics vs. atypical antipsychotics in the treatment of acute mania in a natural setting. Int J Neuropsychopharmacol 2006;9(5):529-37. PMID:16191207
82. Lieberman JA, Philipp M, Kong L. Efficacy and safety of clozapine versus chlorpromazine in first episode psychosis: result of a 52-week randomized double-blind trial. Schizophr Res 2001;49:236.
83. Lipkovich IA, Deberdt W, Csernansky JG, et al. Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: a path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. BMC Psychiatry 2009;9:44. PMID:19602273
84. Loebel AD, Khanna S, Rajadhyaksha. Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. J Clin Psychiatry 2007;(9):1333-8. PMID:17915970
85. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Archives of General Psychiatry 2001;58(12):1172-6. PMID:11735847
86. Mahmoud R, Engelhart L, Ollendorf D, et al. The risperidone outcomes study of effectiveness (ROSE): a model for evaluating strategies in typical psychiatric practice. J Clin Psychiatry 1999;60(Suppl 3):42-8. PMID:10073377
87. Mahmoud RA, Engelhart LM, Janagap CC, et al. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: symptoms, quality of life and resource use under customary clinical care. Clin Drug Invest 2004;24(5):275-86. PMID:17503889
88. Malla AK, Norman RMG, Scholten DJ, et al. A comparison of long-term outcome in first-episode schizophrenia following treatment with risperidone or a typical antipsychotic. J Clin Psychiatry 2001;62(3):179-84. PMID:11305704
89. Mann K, Bartels M, Gartner HJ, et al. Differential effects of a new dibenzo-epine neuroleptic compared with haloperidol: results of an open and crossover study. Pharmacopsychiatry 1987;20(4):155-9. PMID:2886997
90. Mari JDJ, Lima MS, Costa AN, et al. The prevalence of tardive dyskinesia after a nine month naturalistic randomized trial comparing olanzapine with conventional treatment for schizophrenia and related disorders. Eur Arch Psychiatry Clin Neurosci 2004;254(6):356-61.

91. McCue RE, Waheed R, Urcuyo L, et al. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. Br J Psychiatry 2006;189:433-40. PMID:17077434
92. Meehan k, Wang H, David S, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26:494-504. PMID:11927174
93. Mehta S, Johnson ML, Chen H, et al. Risk of cerebrovascular adverse events in older adults using antipsychotic agents: a propensity-matched retrospective cohort study. J Clin Psychiatry 2010;71(6):689-98. PMID:20573328
94. Meltzer HY, Bastani B, Kwon KY. A prospective study of clozapine in treatment-resistant schizophrenic patients: preliminary report. Psychopharmacology (Berl) 1989;99:S68-S72. PMID:2813667
95. Meltzer HY, Bobo WV, Lee MA, et al. A randomized trial comparing clozapine and typical neuroleptic drugs in non-treatment-resistant schizophrenia. Psychiatry Res 2010;177(3):286-93. PMID:20378185
96. Miller CH, Mohr F, Umbricht D, et al. The prevalence of acute extrapyramidal signs and symptoms in patients treated with clozapine, risperidone, and conventional antipsychotics. J Clin Psychiatry 1998;59(2):69-75. PMID:9501888
97. Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. J Clin Psychiatry 2001;62(12):975-80. PMID:11780879
98. Mojtabai R, Lavelle J, Joseph GP, et al. Atypical antipsychotics in first admission schizophrenia: medication continuation and outcomes. Schizophr Bull 2003;29(3):519-30. PMID:14609245
99. Montes JM, Ciudad A, Gascon J, et al. Safety, effectiveness, and quality of life of olanzapine in first-episode schizophrenia: a naturalistic study. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(4):667-74. PMID:12787855
100. Montgomery J, Winterbottom E, Jessani M, et al. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. J Clin Psychiatry 2004;65(11):1491-8. PMID:15554761
101. Moore DB, Kelly DL, Sherr JD, et al. Rehospitalization rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. Am J Health-Syst Pharm 1998;55(24:Suppl 4):S17-S19. PMID:9872689
102. Murasaki M. Efficacy and tolerability of quetiapine compared with haloperidol in patients with schizophrenia. Int J Neuropsychopharmacol 2000;(Suppl 1):S150.
103. Nakonezny PA, Byerly MJ. Electronically monitored adherence in outpatients with schizophrenia or schizoaffective disorder: a comparison of first- vs. second-generation antipsychotics. Schizophr Res 2006;82(1):107-14. PMID:16376522
104. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. Neuropsychopharmacology 2010;35(9):1997-2004. PMID:20520598
105. Novick D, Haro JM, Bertsch J, et al. Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia: Thirty-six-month results from the European schizophrenia outpatient health outcomes study. J Clin Psychopharmacol 2010;Vol.30(5):531-40. PMID:20814320
106. Novick D, Haro JM, Perrin E, et al. Tolerability of outpatient antipsychotic treatment: 36-month results from the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. Eur Neuropsychopharmacol 2009;(8):542-50. PMID:19500949
107. Novick D, Haro JM, Suarez D, et al. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. Schizophr Res 2009;108(1-3):223-30. PMID:19500949
108. Peacock L, Solgaard T, Lublin H, et al. Clozapine versus typical antipsychotics: a retro- and prospective study of extrapyramidal side effects. Psychopharmacology (Berl) 1996;124(1-2):188-96. PMID:8935815
109. Peralta V, Campos MS, de Jalon EG, et al. DSM-IV catatonia signs and criteria in first-episode, drug-naive, psychotic patients: psychometric validity and response to antipsychotic medication. Schizophr Res 2010;118(1-3):168-75. PMID:20071147
110. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. New Engl J Med 2009;360(3):225-35. PMID:19144938
111. Ritsner MS, Gibel A. The effectiveness and predictors of response to antipsychotic agents to treat impaired quality of life in schizophrenia: a 12-month naturalistic follow-up study with implications for confounding factors, antidepressants, anxiolytics, and mood stabilizers. Prog Neuropsychopharmacol Biol Psychiatry 2006;30(8):1442-52.
112. Rollnik JD, Borsutzky M, Huber TJ, et al. Short-term cognitive improvement in schizophrenics treated with typical and atypical neuroleptics. Neuropsychobiology 2002;45(2):74-80. PMID:11893863
113. Rosebush PI, Mazurek MF. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. Neurology 1999;52(4):782-5. PMID:10078728
114. Rothschild AJ, Bates KS, Boehringer KL, et al. Olanzapine response in psychotic depression. J Clin Psychiatry 1999;60(2):116-8. PMID:10084638
115. Sacchetti E, Turrina C, Parrinello G, et al. Incidence of diabetes in a general practice population: a database cohort study on the relationship with haloperidol, olanzapine, risperidone or quetiapine exposure. Int Clin Psychopharmacol 2005;20(1):33-7. PMID:15602114

116. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159(4):561-6. PMID:11925293
117. Shafti SS SB. Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double-blind trial. J Clin Psychopharmacol 2010;(1):44-7. PMID:20075647
118. Shi L, Juarez R, Hackworth J, et al. Open-label olanzapine treatment in bipolar I disorder: clinical and work functional outcomes. Curr Med Res Opin 2006;22(5):961-6. PMID:16709317
119. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology 2004;29(1):133-45. PMID:14583740
120. Silva de LM, de Jesus MJ, Breier A, et al. Quality of life in schizophrenia: a multicenter, randomized, naturalistic, controlled trial comparing olanzapine to first-generation antipsychotics. J Clin Psychiatry 2005;66(7):831-8. PMID:16013897
121. Smelson DA, Losonczy MF, Davis CW, et al. Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence. Can J Psychiatry 2002;47(7):671-5. PMID:12355680
122. Stargardt T, Weinbrenner S, Busse R, et al. Effectiveness and cost of atypical versus typical antipsychotic treatment for schizophrenia in routine care. J Mental Health Policy Econ 2008;11(2):89-97. PMID:18509216
123. Tandon R, Marcus RN, Stock EG, et al. A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: Broad Effectiveness Trial With Aripiprazole (BETA). Schizophr Res 2006;84(1):77-89. PMID:16483745
124. Tsirigotis K, Gruszczynski W. Needs and values of outpatients with schizophrenia, treated with classic neuroleptics and risperidone. Arch Psychiatr Psychother 2004;6(3):37-51.
125. Tsirigotis K, Gruszczynski W. Personality functioning of outpatients with schizophrenia treated with classic neuroleptics and risperidone. Arch Psychiatr Psychother 2004;6(3):23-36.
126. Tunis SL, Faries DE, Nyhuis AW, et al. Cost-effectiveness of olanzapine as first-line treatment for schizophrenia: results from a randomized, open-label, I-year trial. Value Health 2006;9(2):77-89. PMID:16626411
127. Van Praag HM, Korf J, Dols LC. Clozapine versus perphenazine: the value of the biochemical mode of action of neuroleptics in predicting their therapeutic activity. Br J Psychiatry 1976;129:547-55. PMID:1000139
128. Velligan DI, Prihoda TJ, Sui D, et al. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. J Clin Psychiatry 2003;64(5):524-31. PMID:12755654
129. Veser FH, Veser BD, McMullan JT, et al. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis: a pilot, randomized, double-blind, placebo-controlled trial. J Psychiatr Pract 2006;12(2):103-8. PMID:16728906
130. Villari V, Rocca P, Fonzo V, et al. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(2):405-13. PMID:17900775
131. Weiden P, Glazer W. Assessment and treatment selection for "revolving door" inpatients with schizophrenia. Psychiatr Q 1997;68(4):377-92. PMID:9355136
132. Wetter TC, Lauer CJ, Gillich G, et al. The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. J Psychiatr Res 1996;30(6):411-9. PMID:9023785
133. Wirz-Justice A, Haug HJ, Cajochen C. Disturbed circadian rest-activity cycles in schizophrenia patients: an effect of drugs? Schizophr Bull 2001;27(3):497-502. PMID:11596850
134. Wittorf A, Sickinger S, Wiedemann G, et al. Neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia: a naturalistic 6-month follow-up study. Arch Clin Neuropsychol 2008;23(3):271-82. PMID:18272323

No Extractable Data Related to Outcomes of Interest

1. Apiquian R, Fresan A, Herrera K, et al. Minimum effective doses of haloperidol for the treatment of first psychotic episode: a comparative study with risperidone and olanzapine. Int J Neuropsychopharmacol 2003;6(4):403-8. PMID:14604455
2. Atmaca M, Kuloglu M, Tezcan E, et al. Weight gain, serum leptin and triglyceride levels in patients with schizophrenia on antipsychotic treatment with quetiapine, olanzapine and haloperidol. Schizophr Res 2003;60(1):99-100. PMID:12505146
3. Bitter I, Czobor P, Dossenbach M, et al. Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO). Eur Psychiatry 2005;20(5-6):403-8. PMID:16084068
4. Brook S, Lucey JV, Gunn KP. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000;61(12):933-41. PMID:11206599

5. Bustillo JR, Lauriello J. Longitudinal follow-up of neurochemical changes during the first year of antipsychotic treatment in schizophrenia patients with minimal previous medication exposure. Schizophr Res 2002;(2-3):313-21. PMID:12409172
6. Bustillo JR, Rowland LM, Jung. Proton magnetic resonance spectroscopy during initial treatment with antipsychotic medication in schizophrenia. Neuropsychopharmacology 2008;(10):2456-66. PMID:18094668
7. Castro AP, Elkis H. Rehospitalization rates of patients with schizophrenia discharged on haloperidol, risperidone or clozapine. Rev Bras Psiquiatr 2007;29(3):207-12. PMID:17891257
8. Ceskova E, Svetska J. Risperidone vs. perphenazine: a double-blind comparison and prolactin plasma levels. Psychiatr Danub 1994;6(3-4):151-5.
9. Chae BJ, Kang BJ. The effect of clozapine on blood glucose metabolism. Hum Psychopharmacol 2001;16(3):265-71. PMID:12404579
10. Classen W, Laux G. Sensorimotor and cognitive performance of schizophrenic inpatients treated with haloperidol, flupenthixol, or clozapine. Pharmacopsychiatry 1988;21(6):295-7. PMID:2907629
11. Crespo-Facorro B, Carrasco-Marin E, Perez-Iglesias R, et al. Interleukin-12 plasma levels in drug-naive patients with a first episode of psychosis: Effects of antipsychotic drugs. Psychiatry Res 2008;Vol.158(2):206-16. PMID:18243335
12. Di SG, Calo S, Amodio G, et al. The use of first generation versus second generation antipsychotics as add-on or as switch treatment and its effect on QTC interval: the Italian experience in a real-world setting. International Journal of Immunopathology & Pharmacology 2011;24(1):225-30.
13. Dossenbach M, Dyachkova Y, Pirildar S, et al. Effects of atypical and typical antipsychotic treatments on sexual function in patients with schizophrenia: 12-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. Eur Psychiatry 2006;21(4):251-8.
14. Dossenbach M, Erol A, el Mahfoud KM, et al. Effectiveness of antipsychotic treatments for schizophrenia: interim 6-month analysis from a prospective observational study (IC-SOHO) comparing olanzapine, quetiapine, risperidone, and haloperidol. J Clin Psychiatry 2004;65(3):312-21. PMID:15096069
15. Esel E, Basturk M, Saffet GA, et al. Effects of olanzapine and haloperidol on serum prolactin levels in male schizophrenic patients. Psychoneuroendocrinology 2001;26(6):641-7. PMID:11403983
16. Garcia-Cabeza I, Gomez JC, Sacristan JA, et al. Subjective response to antipsychotic treatment and compliance in schizophrenia: a naturalistic study comparing olanzapine, risperidone and haloperidol (EFESO Study). BMC Psychiatry 2001;1:7. PMID:11835695
17. Gerlach J, Koppelhus P, Helweg E, et al. Clozapine and haloperidol in a single-blind cross-over trial: therapeutic and biochemical aspects in the treatment of schizophrenia. Acta Psychiatr Scand 1974;50(4):410-24. PMID:4153596
18. Gerlach J, Thorsen K, Fog R. Extrapyramidal reactions and amine metabolites in cerebrospinal fluid during haloperidol and clozapine treatment of schizophrenic patients. Psychopharmacologia 1975;40(4):341-50. PMID:1096218
19. Gerra G, Di PG, D'Amore A, et al. Combination of olanzapine with opioid-agonists in the treatment of heroin-addicted patients affected by comorbid schizophrenia spectrum disorders. Clin Neuropharmacol 2007;30(3):127-35. PMID:17545747
20. Glick ID, Stekoll AH, Hays S. The role of the family and improvement in treatment maintenance, adherence, and outcome for schizophrenia. J Clin Psychopharmacol 2011;Vol.31(1):82-5. PMID:21192148
21. Heh CW, Herrera J, DeMet E, et al. Neuroleptic-induced hypothermia associated with amelioration of psychosis in schizophrenia. Neuropsychopharmacology 1988;1(2):149-56. PMID:3251495
22. Hempel RJ, Tulen JH, van Beveren NJ, et al. Cardiovascular variability during treatment with haloperidol, olanzapine or risperidone in recent-onset schizophrenia. J Psychopharmacol 2009;23(6):697-707. PMID:18562420
23. Herceg M, Jukic V, Vidovic D, et al. Two-year rehospitalization rates of patients with newly diagnosed or chronic schizophrenia on atypical or typical antipsychotic drugs: retrospective cohort study. Croat Med J 2008;49(2):215-23. PMID:18461677
24. Hsu WY, Huang SS, Lee BS, et al. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. J Clin Psychopharmacol 2010;30(3):230-4. PMID:20473056
25. Huang TL, Chen JF. Serum lipid profiles and schizophrenia: effects of conventional or atypical antipsychotic drugs in Taiwan. Schizophr Res 2005;80(1):55-9. PMID:15964176
26. Huang TL, Lu CY. Correlations between weight changes and lipid profile changes in schizophrenic patients after antipsychotics therapy. Chang Gung Med J 2007;30(1):26-32. PMID:17477026
27. Hummer M, Kemmler G, Kurz M, et al. Sexual disturbances during clozapine and haloperidol treatment for schizophrenia. Am J Psychiatry 1999;156(4):631-3. PMID:10200746
28. Jerrell JM, McIntyre RS, Tripathi A. Incidence and costs of cardiometabolic conditions in patients with schizophrenia treated with antipsychotic medications. Clinical Schizophrenia & Related Psychoses 2010;4(3):161-8. PMID:20880826

29. Kapur S, Arenovich T, Agid O, et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. Am J Psychiatry 2005;162(5):939-46. PMID:15863796
30. Kessing LV, Thomsen AF, Mogensen UB, et al. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br J Psychiatry 2010;197(4):266-71. PMID:20884948
31. Lambert M, Schimmelmann BG, Schacht A, et al. Differential 3-year effects of first- versus second-generation antipsychotics on subjective well-being in schizophrenia using marginal structural models. J Clin Psychopharmacol 31[2], 226-230. 2011.
32. Lane HY, Guo SC, Hwang TJ, et al. Effects of olanzapine plasma concentrations on depressive symptoms in schizophrenia: a pilot study. J Clin Psychopharmacol 2002;22(5):530-2. PMID:12352282
33. Lee P, Eung KC, Yoon KC, et al. Long-term, naturalistic treatment with olanzapine, risperidone, quetiapine, or haloperidol monotherapy: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. Int J Psychiatr Clin Pract 2008;12(3):215-27.
34. Liew A, Verma S, Lye YP, et al. Comparing effectiveness of risperidone with first-generation antipsychotic medications in patients with schizophrenia-spectrum disorders. J Psychopharmacol 2010;24(7):973-80.
35. Lindenmayer, Jean Pierre, Smith RC, et al. Hyperglycemia in patients with schizophrenia who are treated with olanzapine. J Clin Psychopharmacol 2001;21(3):351-3. PMID:11386505
36. Marder SR. Risperidone: clinical development: North American results. Clin Neuropharmacol 1992;15(Suppl 93A) PMID:1379883
37. Nechifor M, Vaideanu C, Palamaru I, et al. The influence of some antipsychotics on erythrocyte magnesium and plasma magnesium, calcium, copper and zinc in patients with paranoid schizophrenia. J Am Coll Nutr 2004;23(5):549S-51S. PMID:15466963
38. Olfson M, Marcus SC, scher-Svanum H. Treatment of schizophrenia with long-acting fluphenazine, haloperidol, or risperidone. Schizophr Bull 2007;33(6):1379-87. PMID:17470444
39. Opjordsmoen S, Melle I, Friis S, et al. Stability of medication in early psychosis: a comparison between second-generation and low-dose first-generation antipsychotics. Early Intervention in Psychiatry 2009;3(1):58-65. PMID:21352176
40. Paunovic VR, Timotijevic I, Marinkovic D. Neuroleptic actions on the thyroid axis: different effects of clozapine and haloperidol. Int Clin Psychopharmacol 1991;6(3):133-9. PMID:1806619
41. Potkin SG, Fleming K, Jin Y, et al. Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. J Clin Psychopharmacol 2001;21(5):479-83. PMID:11593072
42. Ravanic DB, Dejanovic SM, Janjic V, et al. Effectiveness of clozapine, haloperidol and chlorpromazine in schizophrenia during a five-year period. Arq Neuro-Psiquiatr 2009;67(2A):195-202. PMID:19547808
43. Remillard S, Pourcher E, Cohen H. Long-term skill proceduralization in schizophrenia. J Int Neuropsychol Soc 2010;16(1):148-56. PMID:19900349
44. Remillard S, Pourcher E, Cohen H. The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: a 1-year follow up study. Schizophr Res 2005;80(1):99-106. PMID:16162401
45. Rizos EN, Papadopoulou A, Laskos E, et al. Reduced serum BDNF levels in patients with chronic schizophrenic disorder in relapse, who were treated with typical or atypical antipsychotics. World J Biol Psychiatry 2010;11(2:Pt 2):251-5.
46. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. New Engl J Med 2011;364(9):842-51. PMID:21366475
47. Schennach-Wolff R, Jager M, Mayr A, et al. Predictors of response and remission in the acute treatment of first-episode schizophrenia patients--Is it all about early response? Eur Neuropsychopharmacol 2011;21(5):370-378.
48. Schuhmacher A, Mossner R, Quednow BB, et al. Influence of 5-HT3 receptor subunit genes HTR3A, HTR3B, HTR3C, HTR3D and HTR3E on treatment response to antipsychotics in schizophrenia. Pharmacogenet Genomics 2009;19(11):843-51. PMID:19794330
49. Spivak B, Shabash E, Sheitman B, et al. The effects of clozapine versus haloperidol on measures of impulsive aggression and suicidality in chronic schizophrenia patients: an open, nonrandomized, 6-month study. J Clin Psychiatry 2003;64(7):755-60. PMID:12934974
50. Stoner SC, Wehner Lea JS, Dubisar BM, et al. Impact of clozapine versus haloperidol on conditional release time and rates of revocation in a forensic psychiatric population. J Pharm Technol 2002;18(4):182-6.
51. Strassnig M, Miewald J, Keshavan M, et al. Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophr Res 2007;93(1-3):90-8. PMID:17478082
52. Stroup TS, Lieberman JA, McEvoy JP, et al. Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res 2009;107(1):1-12. PMID:19027269
53. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 2009;374(9690):620-7. PMID:19595447

54. Tiihonen J, Wahlbeck K, Lonnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ: British Medical Journal 2006;333(7561):224.
55. Tiwari AK, Zai CC, Likhodi O, et al. A common polymorphism in the cannabinoid receptor 1 (CNR1) gene is associated with antipsychotic-induced weight gain in Schizophrenia. Neuropsychopharmacology 2010;35(6):1315-24. PMID:20107430
56. Tiwari AK, Zai CC, Meltzer HY, et al. Association study of polymorphisms in insulin induced gene 2 (INSIG2) with antipsychotic-induced weight gain in European and African-American schizophrenia patients. Hum Psychopharmacol 2010;25(3):253-9. PMID:20373477
57. Treuer T, Martenyi F, Saylan M, et al. Factors associated with achieving minimally symptomatic status by patients with schizophrenia: results from the 3-year intercontinental schizophrenia outpatients health outcomes study.[Erratum appears in Int J Clin Pract. 2010 Sep;64(10):1459]. Int J Clin Pract 2010;64(6):697-706.
58. Zahn TP, Pickar D, Haier RJ. Effects of clozapine, fluphenazine, and placebo on reaction time measures of attention and sensory dominance in schizophrenia. Schizophr Res 1994;13(2):133-44. PMID:7986770

Unavailable for Review Through Library Services

1. Atmaca M. The comparison of efficacy of quetiapine and haloperidol in a group of schizophrenic patients with comorbid depressive disorder. Anatol J Psychiatry 2002;(1):14-9.
2. Beasley C. Safety Overview of Olanzapine. Xth World Congress of Psychiatry, Madrid, Spain 2000.
3. Borison R. Risperidone versus haloperidol versus placebo in the treatment of schizophrenia. Clin Report 1991.
4. Cohen BM, Keck PE, Satlin A. Prevalence and severity of akathisia in patients on clozapine. Biol Psychiatry 1991;29:1215-9. PMID:1888803
5. ddington DE, Arvanitis LA. 'Seroquel' (quetiapine): an atypical antipsychotic: results from a multiple fixed dose, placebo-controlled study. Schizophrenia 1996;1996-9.
6. He J. A comparative trial of olanzapine versus chlorpromazine in the treatment of schizophrenia. Shandong Arch Psychiatry 2003;(2):78-80.
7. Liang J. A comparative study of aripiprazole and haloperidol on quality of life in patients with schizophrenia. Med Inf 2006;(8):1406-9.
8. Lieberman JA, Charles C. Effect of olanzapine versus haloperidol on brain pathomorphology in first-episode psychosis. 156th Annual Meeting of the American Psychiatric Association 2003.
9. Loebel AD, Warrington L. Remission in schizophrenia: a comparison of 2 dose regimens of ziprasidone vs haloperidol treatment in a 40-week core and 3-year double-blind extension study. Proceedings of the 159th Annual Meeting of the American Psychiatric Association 2006;25.
10. Lu BH, Su XR, Xie BQ. A comparative study of loxapine and risperidone in the treatment of schizophrenia. Shandong Jingshen Yixue 2006;(2):122-3.
11. Qian C. Analysis of therapeutic effect for schizophrenia with risperidone and perphenazine. Acta Uni Med Nahui 2001;(3):227-9.
12. Ren Q. A comparative study between perphenazine and risperidone on the effect on the life quality of the patients with schizophrenia. Chin J Behav Med Sci 2002;(1):32-3.
13. Rosebush P, Mazurek M. Olanzapine versus haloperidol in randomized trials of first-episode patients with schizophrenia. Stanley Found Res Prog 2000.
14. Tatossian A. Comparitive double-blind trial of the efficacy of risperidone, haloperidol and levomepromazine (methotrimeprazine) in patients with an acute exacerbation of schizophrenia presenting psychotic anxiety symptoms. Clin Report 1991.
15. Tran P. Olanzapine vs haloperidol: results of a large multi-centre international trial. Schizophrenia 1996.
16. Zahn TP, Pickar D. Autonomic effects of clozapine in schizophrenia: comparison with placebo and fluphenazine. Biol Psychiatry 1993;34(1-2):3-12. PMID:8104043
17. Zhang Z. Comparative clinic analysis of risperidone and haloperidol for treatment of schizophrenic negative symptoms. Int Chin Neuropsychiatry Med J 2004;(1):37-8.

Appendix D. List of Companion Studies

A total of 146 articles were companions to the included studies.

1. Addington DE, Mohamed S, Rosenheck RA, et al. Impact of second-generation antipsychotics and perphenazine on depressive symptoms in a randomized trial of treatment for chronic schizophrenia. J Clin Psychiatry 2011;72(1):75-80. PMID:20868641
2. Andrezina R, Marcus RN, Oren DA, et al. Intramuscular aripiprazole or haloperidol and transition to oral therapy in patients with agitation associated with schizophrenia: sub-analysis of a double-blind study. Curr Med Res Opin 2006;22(11):2209-19. PMID:17076982
3. Arango C, Breier A, McMahon R, et al. The relationship of clozapine and haloperidol treatment response to prefrontal, hippocampal, and caudate brain volumes. Am J Psychiatry 2003;160(8):1421-7. PMID:12900303
4. Arango C, Summerfelt A, Buchanan RW. Olanzapine effects on auditory sensory gating in schizophrenia. Am J Psychiatry 2003;160(11):2066-8. PMID:14594761
5. Ascher-Svanum H, Stensland M, Zhao Z, et al. Acute weight gain, gender, and therapeutic response to antipsychotics in the treatment of patients with schizophrenia. BMC Psychiatry 2005;5:3. PMID:15649317
6. Baymiller SP, Ball P, McMahon RP, et al. Serum glucose and lipid changes during the course of clozapine treatment: the effect of concurrent beta-adrenergic antagonist treatment. Schizophr Res 2003;59(1):49-57. PMID:12413642
7. Baymiller SP, Ball P, McMahon RP, et al. Weight and blood pressure change during clozapine treatment. Clin Neuropharmacol 2002;25(4):202-6. PMID:12151907
8. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002;159(6):1018-28. PMID:12042192
9. Boter H, Peuskens J, Libiger J, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). Schizophr Res 2009;115(2-3):97-103. PMID:19819114
10. Boulay LJ. Contrasting the effects of haloperidol and olanzapine on attention and working memory in schizophrenia: a double-blind flexible dose study [dissertation] 2004.
11. Bowden CL, Myers JE, Grossman F, et al. Risperidone in combination with mood stabilizers: a 10-week continuation phase study in bipolar I disorder. J Clin Psychiatry 2004;65(5):707-14. PMID:15163260
12. Breier A, Buchanan RW, Waltrip RW, et al. The effect of clozapine on plasma norepinephrine: relationship to clinical efficacy. Neuropsychopharmacology 1994;10(1):1-7. PMID:8179790
13. Breier A, Hamilton SH. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. Biol Psychiatry 1999;45(4):403-11. PMID:10071708
14. Buchanan RW, Breier A, Kirkpatrick B, et al. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am J Psychiatry 1998;155(6):751-60. PMID:9619146
15. Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol Psychiatry 1994;36(11):717-25. PMID:7858067
16. Buckley PF, Goldstein JM, Emsley RA. Efficacy and tolerability of quetiapine in poorly responsive, chronic schizophrenia. Schizophr Res 2004;(2-3):143-50. PMID:15061246
17. Bustillo JR, Buchanan RW, Irish D, et al. Differential effect of clozapine on weight: a controlled study. Am J Psychiatry 1996;153(6):817-9. PMID:8633697
18. Chengappa KN, Goldstein JM, Greenwood M, et al. A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. Clin Ther 2003;25(2):530-41. PMID:12749512
19. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. J Clin Psychopharmacol 1995;15(1:Suppl 1):36S-44S. PMID:7537286
20. Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized, open-label study data. J Clin Psychiatry 2006;67(4):638-42. PMID:16669729
21. Cramer J, Rosenheck R, Xu W, et al. Detecting improvement in quality of life and symptomatology in schizophrenia. Schizophr Bull 2001;27(2):227-34. PMID:11354590
22. Crawford AM, Beasley CM, Jr., Tollefson GD. The acute and long-term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations. Schizophr Res 1997;26(1):41-54. PMID:9376336
23. Crespo-Facorro B, Carrasco-Marin E, Perez-Iglesias R, et al. Interleukin-12 plasma levels in drug-naive patients with a first episode of psychosis: effects of antipsychotic drugs. Psychiatry Res 2008;158(2):206-16. PMID:18243335

24. Crespo-Facorro B, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year followup comparison. J Clin Psychiatry 2009;70(5):717-29. PMID:19389335
25. Crespo-Facorro B, Roiz-Santianez R, Perez-Iglesias R, et al. Effect of antipsychotic drugs on brain morphometry: a randomized controlled one-year followup study of haloperidol, risperidone and olanzapine. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1936-43. PMID:18930104
26. Crespo-Facorro B, rrez-Iglesias R, Mata I, et al. Relapse prevention and remission attainment in first-episode non-affective psychosis. A randomized, controlled 1-year followup comparison of haloperidol, risperidone and olanzapine. J Psychiatr Res 2011;45(6):763-9. PMID:21106207
27. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15(4):243-9. PMID:7593706
28. Czobor P, Volavka J, Sheitman B, et al. Antipsychotic-induced weight gain and therapeutic response: a differential association. J Clin Psychopharmacol 2002;22(3):244-51. PMID:12006893
29. Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. Schizophr Res 2008;105(1-3):175-87. PMID:18775645
30. Docherty JP, Baker RA, Eudicone J, et al. Effect of aripiprazole versus haloperidol on PANSS Prosocial items in early-episode patients with schizophrenia. Schizophr Res 2010;120(1-3):199-203. PMID:20547037
31. Dossenbach MR, Folnegovic-Smalc V, Hotujac L, et al. Double-blind, randomized comparison of olanzapine versus fluphenazine in the long-term treatment of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2004;28(2):311-8. PMID:14751428
32. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006;163(4):743-5. PMID:16585455
33. Emsley R, Turner HJ, Schronen J, et al. A single-blind, randomized trial comparing quetiapine and haloperidol in the treatment of tardive dyskinesia. J Clin Psychiatry 2004;65(5):696-701. PMID:15163258
34. Emsley RA, Buckley P. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. J Psychopharmacol 2003;(2):210-5. PMID:12870569
35. Fakra E, Salgado-Pineda P, Besnier N, et al. Risperidone versus haloperidol for facial affect recognition in schizophrenia: findings from a randomized study. World J Biol Psychiatry 2009;10(4:Pt 3):-28. PMID:17853271
36. Gaebel W, Moller HJ, Buchkremer G, et al. Pharmacological long-term treatment strategies in first episode schizophrenia: study design and preliminary results of an ongoing RCT within the German Research Network on Schizophrenia. Eur Arch Psychiatry Clin Neurosci 2004;254(2):129-40. PMID:15146342
37. Gaebel W, Riesbeck M, von Wilmsdorff M, et al. Drug attitude as predictor for effectiveness in first-episode schizophrenia: Results of an open randomized trial (EUFEST). Eur Neuropsychopharmacol 2010;20(5):310-6. PMID:20202800
38. Gaebel W, Riesbeck M, Wolwer W, et al. Maintenance treatment with risperidone or low-dose haloperidol in first-episode schizophrenia: 1-year results of a randomized controlled trial within the German Research Network on Schizophrenia. J Clin Psychiatry 2007;68(11):1763-74. PMID:18052570
39. Glynn SM, Marder SR, Liberman RP, et al. Supplementing clinic-based skills training with manual-based community support sessions: effects on social adjustment of patients with schizophrenia. Am J Psychiatry 2002;159(5):829-37. PMID:11986138
40. Goldstein JM, Cohen LS, Horton NJ, et al. Sex differences in clinical response to olanzapine compared with haloperidol. Psychiatry Res 2002;110(1):27-37. PMID:12007591
41. Gomez JC, Crawford AM. Superior efficacy of olanzapine over haloperidol: analysis of patients with schizophrenia from a multicenter international trial. J Clin Psychiatry 2001;62(Suppl 11) PMID:11232753
42. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. Schizophr Res 2006;86(1-3):234-43. PMID:16887334
43. Green AI, Tohen MF, Hamer RM, et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res 2004;66(2-3):125-35. PMID:15061244
44. Green MF, Marder SR, Glynn SM, et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol Psychiatry 2002;51(12):972-8. PMID:12062881
45. Green MF, Marshall BD, Jr., Wirshing WC, et al. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? Am J Psychiatry 1997;154(6):799-804. PMID:9167507
46. Hamilton SH, Edgell ET, Revicki DA, et al. Functional outcomes in schizophrenia: a comparison of olanzapine and haloperidol in a European sample. Int Clin Psychopharmacol 2000;15(5):245-55. PMID:10993126
47. Hamilton SH, Revicki DA, Edgell ET, et al. Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia: results from a randomized clinical trial. Pharmacoeconomics 1999;(5):469-80. PMID:10537964

48. Hamilton SH, Revicki DA, Genduso LA, et al. Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. Neuropsychopharmacology 1998;18(1):41-9. PMID:9408917
49. Harvey PD, Pappadopulos E, Lombardo I, et al. Reduction of functional disability with atypical antipsychotic treatment: a randomized long term comparison of ziprasidone and haloperidol. Schizophr Res 2009;115(1):24-9. PMID:19189878
50. Harvey PD, Rabinowitz J, Eerdekens M, et al. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry 2005;162(10):1888-95. PMID:16199835
51. Horowitz, Terri Lynn. Comparative neuropsychological effects of clozapine, risperidone, and haloperidol in treatment-refractory schizophrenia [dissertation] 2001.
52. Inada T, Yagi G, Miura S. Extrapyramidal symptom profiles in Japanese patients with schizophrenia treated with olanzapine or haloperidol. Schizophr Res 2002;57(2-3):227-38. PMID:12223254
53. Jakovljevic M, Pivac N, Mihaljevic-Peles A, et al. The effects of olanzapine and fluphenazine on plasma cortisol, prolactin and muscle rigidity in schizophrenic patients: a double blind study. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(2):399-402. PMID:17126974
54. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: results of a US multicenter trial. Psychopharmacology (Berl) 1989;99(Suppl):60-3.
55. Kane JM, Kim E, Kan HJ, et al. Comparative utility of aripiprazole and haloperidol in schizophrenia: post hoc analysis of two 52-week, randomized, controlled trials. Appl Health Econ Health Policy 2009;7(2):109-19. PMID:19731968
56. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Archives of General Psychiatry 2007;64(6):633-47. PMID:17548746
57. Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004;161(6):985-95. PMID:15169686
58. Keefe RS, Seidman LJ, Christensen BK, et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry 2006;59(2):97-105. PMID:16140282
59. Kelly DL, Conley RR. A randomized double-blind 12-week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. Psychoneuroendocrinology 2006;31(3):340-6. PMID:16198059
60. Kelly DL, Conley RR. Thyroid function in treatment-resistant schizophrenia patients treated with quetiapine, risperidone, or fluphenazine. J Clin Psychiatry 2005;66(1):80-4. PMID:15669892
61. Kern RS, Green MF, Marshall BD, Jr., et al. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. Biol Psychiatry 1998;44(8):726-32. PMID:9798076
62. Kern RS, Green MF, Marshall J, et al. Risperidone versus haloperidol on secondary memory: can newer medications aid learning? Schizophr Bull 1999;25(2):223-32. PMID:10416728
63. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry 2001;(2):92-100. PMID:11247108
64. Kinon BJ, Roychowdhury SM, Milton DR, et al. Effective resolution with olanzapine of acute presentation of behavioral agitation and positive psychotic symptoms in schizophrenia. J Clin Psychiatry 2001;62(Suppl 21) PMID:11232746
65. Krakowski M, Czobor P, Citrome L. Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol. Schizophr Res 2009;110(1-3):95-102. PMID:19269139
66. Krakowski MI, Czobor P, Nolan KA. Atypical antipsychotics, neurocognitive deficits, and aggression in schizophrenic patients. J Clin Psychopharmacol 2008;28(5):485-93. PMID:18794642
67. Krakowski, Menahem I, Czobor P. A prospective longitudinal study of cholesterol and aggression in patients randomized to clozapine, olanzapine, and haloperidol. J Clin Psychopharmacol 2010;30(2):198-200. PMID:20520296
68. Lee SM, Chou YH, Li MH, et al. Effects of haloperidol and risperidone on cerebrohemodynamics in drug-naive schizophrenic patients. J Psychiatr Res 2008;42(4):328-35. PMID:17412363
69. Levine SZ, Rabinowitz J. Trajectories and antecedents of treatment response over time in early-episode psychosis. Schizophr Bull 2010;36(3):624-32. PMID:18849294
70. Liberman RP, Gutkind D, Mintz J, et al. Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. Compr Psychiatry 2002;43(6):469-73. PMID:12439835
71. Lieberman JA, Tollefson GD, Charles. Antipsychotic drug effects on brain morphology in first-episode psychosis. Archives of General Psychiatry 2005;(4):361-70. PMID:15809403
72. Lindenmayer JP, Czobor P. V. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. The American Journal of Psychiatry 2003;(2):290-6. PMID:12562575
73. Lindenmayer JP, Czobor P.V. Effects of atypical antipsychotics on the syndromal profile in treatment-resistant schizophrenia. J Clin Psychiatry 2004;(4):551-6. PMID:15119920

74. Lindstrom E, von KL. Changes in single symptoms and separate factors of the schizophrenic syndrome after treatment with risperidone or haloperidol. Pharmacopsychiatry 1994;27(3):108-13. PMID:7521534
75. McEvoy JP, Johnson J, Perkins D, et al. Insight in first-episode psychosis. Psychol Med 2006;36(10):1385-93. PMID:16740175
76. McEvoy JP. Efficacy of risperidone on positive features of schizophrenia. J Clin Psychiatry 1994;55(Suppl 21) PMID:7520904
77. McGurk SR, Green MF, Wirshing WC, et al. Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. Schizophr Res 2004;68(2-3):225-33. PMID:15099605
78. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res 2008;101(1-3):273-86. PMID:18258416
79. Miceli JJ, Tensfeldt TG, Shiovitz T, et al. Effects of oral ziprasidone and oral haloperidol on QTc interval in patients with schizophrenia or schizoaffective disorder. Pharmacotherapy 2010;30(2):127-35. PMID:20099987
80. Milas DZ, Ljubin T. Some memory span functions and motor speed in schizophrenics treated with olanzapine versus fluphenazine. Psychiatr Danub 1999;(1-2):55-9.
81. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomized trial. Br J Psychiatry 2008;(4):279-88. PMID:18827289
82. Moller HJ, Bauml J, Ferrero F, et al. Risperidone in the treatment of schizophrenia: results of a study of patients from Germany, Austria, and Switzerland. Eur Arch Psychiatry Clin Neurosci 1997;247(6):291-6. PMID:9477007
83. Moller HJ, Muller H, Borison RL, et al. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients: a re-evaluation of the North American risperidone study. Eur Arch Psychiatry Clin Neurosci 1995;245(1):45-9. PMID:7540426
84. Mossner R, Schuhmacher A, hn KU, et al. Functional serotonin 1A receptor variant influences treatment response to atypical antipsychotics in schizophrenia. Pharmacogenet Genomics 2009;19(1):91-4. PMID:18849890
85. Penn DL, Keefe RS, Davis SM, et al. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr Res 2009;115(1):17-23. PMID:19766459
86. Perez-Iglesias R, Crespo-Facorro B, Amado JA, et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. J Clin Psychiatry 2007;68(11):1733-40. PMID:18052567
87. Perez-Iglesias R, Crespo-Facorro B, Martinez-Garcia O, et al. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naive population. Schizophr Res 2008;99(1-3):13-22. PMID:18053689
88. Perez-Iglesias R, Mata I, Pelayo-Teran JM, et al. Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naive population. Schizophr Res 2009;107(2-3):115-21. PMID:18993033
89. Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, et al. Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment. J Clin Psychopharmacol 2008;28(3):289-95. PMID:18480685
90. Perkins D, Lieberman J, Gu H, et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004;185:18-24. PMID:15231551
91. Perkins DO, Johnson JL, Hamer RM, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006;83(1):53-63. PMID:16529910
92. Perlick DA, Rosenheck RA, Kaczynski R, et al. Association of symptomatology and cognitive deficits to functional capacity in schizophrenia. Schizophr Res 2008;99(1-3):192-9. PMID:17851042
93. Perlick DA, Rosenheck RA, Kaczynski R, et al. Impact of antipsychotic medication on family burden in schizophrenia: longitudinal results of CATIE trial. Schizophr Res 2010;116(2-3):118-25. PMID:19864114
94. Perry PJ, Lund BC, Sanger T, et al. Olanzapine plasma concentrations and clinical response: acute phase results of the North American Olanzapine Trial. J Clin Psychopharmacol 2001;21(1):14-20. PMID:11199942
95. Purdon SE, Woodward N. Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. Psychopharmacology (Berl) 2003;(3-4):390-7. PMID:12827347
96. Rabinowitz J, Davidson M. Risperidone versus haloperidol in long-term hospitalized chronic patients in a double blind randomized trial: a post hoc analysis. Schizophr Res 2001;50(1-2):89-93. PMID:11378317
97. Rabinowitz J, Harvey PD, Eerdekens M, et al. Premorbid functioning and treatment response in recent-onset schizophrenia. Br J Psychiatry 2006;189:31-5. PMID:16816303
98. Rabinowitz J, Hornik T, Davidson M. Rapid onset of therapeutic effect of risperidone versus haloperidol in a double-blind randomized trial. J Clin Psychiatry 2001;62(5):343-6. PMID:11411815
99. Resnick SG, Rosenheck RA, Canive JM, et al. Employment outcomes in a randomized trial of second-generation antipsychotics and perphenazine in the treatment of individuals with schizophrenia. J Behav Health Serv Res 2008;35(2):215-25. PMID:18246429

100. Revicki DA, Genduso LA, Hamilton SH, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and other psychotic disorders: quality of life and clinical outcomes of a randomized clinical trial. Qual Life Res 1999;(5):417-26. PMID:10474283
101. Rosenheck R, Chang S, Choe Y, et al. Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. J Clin Psychiatry 2000;61(5):382-6. PMID:10847315
102. Rosenheck R, Cramer J, Jurgis G, et al. Clinical and psychopharmacologic factors influencing family burden in refractory schizophrenia. J Clin Psychiatry 2000;61(9):671-6. PMID:11030488
103. Rosenheck R, Dunn L, Peszke M, et al. Impact of clozapine on negative symptoms and on the deficit syndrome in refractory schizophrenia. Am J Psychiatry 1999;156(1):88-93. PMID:9892302
104. Rosenheck R, Evans D, Herz L, et al. How long to wait for a response to clozapine: a comparison of time course of response to clozapine and conventional antipsychotic medication in refractory schizophrenia. Schizophr Bull 1999;25(4):709-19. PMID:10667741
105. Rosenheck R, Lawson W, Crayton J, et al. Predictors of differential response to clozapine and haloperidol. Biol Psychiatry 1998;44(6):475-82. PMID:9777179
106. Rosenheck R, Tekell J, Peters J, et al. Does participation in psychosocial treatment augment the benefit of clozapine? Archives of General Psychiatry 1998;55(7):618-25. PMID:9672052
107. Rosenheck RA, Davis VG, Davis SM, et al. Can a nonequivalent choice of dosing regimen bias the results of flexible dose double blind trials? The CATIE schizophrenia trial. Schizophr Res 2009;113(1):12-8. PMID:19545976
108. Saddichha S M. Diabetes and schizophrenia; effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. Acta Psychiatr Scand 2008;(5):342-7. PMID:18307585
109. Saddichha S M. Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in India: a randomized, double-blind, controlled, prospective study. J Clin Psychiatry 2007;(11):1793-8. PMID:18052574
110. Saddichha S, Manjunatha N, Ameen S, et al. Metabolic syndrome in first episode schizophrenia: a randomized double-blind controlled, short-term prospective study. Schizophr Res 2008;101(1-3):266-72. PMID:18262771
111. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999;156(1):79-87. PMID:9892301
112. Schooler NR. Negative symptoms in schizophrenia: assessment of the effect of risperidone. J Clin Psychiatry 1994;55(Suppl 5):May-27. PMID:7520905
113. Schuhmacher A, Mossner R, Quednow BB, et al. Influence of 5-HT3 receptor subunit genes HTR3A, HTR3B, HTR3C, HTR3D and HTR3E on treatment response to antipsychotics in schizophrenia. Pharmacogenet Genomics 2009;19(11):843-51. PMID:19794330
114. Shi L, Namjoshi MA, Zhang F, et al. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. Int Clin Psychopharmacol 2002;17(5):227-37. PMID:12177585
115. Simpson GM, Lindenmayer JP. Extrapyramidal symptoms in patients treated with risperidone. J Clin Psychopharmacol 1997;(3):194-201. PMID:9169965
116. Stahl SM, Malla A, Newcomer JW, et al. A post hoc analysis of negative symptoms and psychosocial function in patients with schizophrenia: A 40-week randomized, double-blind study of ziprasidone versus haloperidol followed by a 3-year double-blind extension trial. J Clin Psychopharmacol 2010;30(4):425-30. PMID:20571437
117. Stauffer VL, Case M, Kinon BJ, et al. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res 2011;187(1-2):42-8. PMID:21168920
118. Strakowski SM, Johnson JL, DelBello MP, et al. Quality of life during treatment with haloperidol or olanzapine in the year following a first psychotic episode. Schizophr Res 2005;78(2-3):161-9. PMID:15950436
119. Stroup TS. Heterogeneity of treatment effects in schizophrenia. Am J Med 2007;120(4:Suppl 1):26-31. PMID:17403379
120. Sugar CA, James GM, Lenert LA, et al. Discrete state analysis for interpretation of data from clinical trials. Med Care 2004;42(2):183-96. PMID:14734956
121. Swanson JW, Swartz MS, Van Dorn RA, et al. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. Br J Psychiatry 2008;193(1):37-43. PMID:18700216
122. Swartz MS, Perkins DO, Stroup TS, et al. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. The American Journal of Psychiatry 2007;(3):428-36. PMID:17329467
123. Swartz MS, Wagner HR, Swanson JW, et al. The effectiveness of antipsychotic medications in patients who use or avoid illicit substances: results from the CATIE study. Schizophr Res 2008;100(1-3):39-52. PMID:18191383
124. Tamayo JM, Mazzotti G, Tohen M, et al. Outcomes for Latin American versus White patients suffering from acute mania in a randomized, double-blind trial comparing olanzapine and haloperidol. J Clin Psychopharmacol 2007;27(2):126-34. PMID:17414234
125. Thompson PM, Bartzokis G, Hayashi KM, et al. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cereb Cortex 2009;19(5):1107-23. PMID:18842668

126. Tohen M, Zhang F, Keck PE, et al. Olanzapine versus haloperidol in schizoaffective disorder, bipolar type. J Affective Disord 2001;67(1-3):133-40. PMID:11869760
127. Tollefson GD, Sanger TM, Andersen SW. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. 11th European College of Neuropsychopharmacology Congress 1998; PMID:9510219
128. Tollefson GD, Sanger TM, Beasley CM, et al. A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998;43(11):803-10. PMID:9611669
129. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Archives of General Psychiatry 1998;55(3):250-8. PMID:9510219
130. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997;154(4):466-74. PMID:9090332
131. Tran PV, Tollefson GD, Sanger TM, et al. Olanzapine versus haloperidol in the treatment of schizoaffective disorder: acute and long-term therapy. Br J Psychiatry 1999;174:15-22. PMID:10211146
132. Tunis SL, Croghan TW, Heilman DK, et al. Reliability, validity, and application of the medical outcomes study 36-item short-form health survey (SF-36) in schizophrenic patients treated with olanzapine versus haloperidol. Med Care 1999;37(7):678-91. PMID:10424639
133. Umbricht DS, Wirshing WC, Wirshing DA, et al. Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. J Clin Psychiatry 2002;63(5):420-4. PMID:12019667
134. Volavka J, Czobor P, Cooper TB, et al. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychiatry 2004;65(1):57-61. PMID:14744169
135. Volavka J, Czobor P, Nolan K, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacol 2004;24(2):225-8. PMID:15206671
136. Wilms G, Van OC, Baert AL, et al. Ventricular enlargement, clinical correlates and treatment outcome in chronic schizophrenic inpatients. Acta Psychiatr Scand 1992;85(4):306-12. PMID:1375802
137. Wright P, Lindborg SR, Birkett M, et al. Intramuscular olanzapine and intramuscular haloperidol in acute schizophrenia: antipsychotic efficacy and extrapyramidal safety during the first 24 hours of treatment. Can J Psychiatry 2003;48(11):716-21. PMID:14733451
138. Wright P, Meehan K, Birkett M, et al. A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. Clin Ther 2003;25(5):1420-8. PMID:12867218
139. Zhang XY, Zhou DF, Cao LY, et al. Changes in serum interleukin-2, -6, and -8 levels before and during treatment with risperidone and haloperidol: relationship to outcome in schizophrenia. J Clin Psychiatry 2004;65(7):940-7. PMID:15291683
140. Zhang XY, Zhou DF, Cao LY, et al. Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 2005;30(8):1532-8. PMID:15886721
141. Zhang XY, Zhou DF, Cao LY, et al. Prolactin levels in male schizophrenic patients treated with risperidone and haloperidol: a double-blind and randomized study. Psychopharmacology (Berl) 2005;178(1):35-40. PMID:15289996
142. Zhang XY, Zhou DF, Cao LY, et al. The interaction between superoxide dismutase and prolactin is involved in response to haloperidol and risperidone treatment in schizophrenia: a double-blind and randomized study. J Clin Psychopharmacol 2006;26(1):103-5. PMID:16415724
143. Zhang XY, Zhou DF, Qi LY, et al. Superoxide dismutase and cytokines in chronic patients with schizophrenia: association with psychopathology and response to antipsychotics. Psychopharmacology (Berl) 2009;204(1):177-84. PMID:19139851
144. Zipursky RB, Christensen BK, Daskalakis Z, et al. Treatment response to olanzapine and haloperidol and its association with dopamine D receptor occupancy in first-episode psychosis. Can J Psychiatry 2005;50(8):462-9. PMID:16127964
145. Zipursky RB, Gu H, Green AI, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry 2005;187:537-43. PMID:16319406
146. Zuo L, Luo X, Krystal JH, et al. The efficacies of clozapine and haloperidol in refractory schizophrenia are related to DTNBP1 variation. Pharmacogenet Genomics 2009;19(6):437-46. PMID:19369910

Appendix E. Risk of Bias Assessment for Randomized Controlled Trials and Nonrandomized Controlled Trials

Guidelines and Decision Rules for Risk of Bias Assessments

Sequence generation:

- If computer-generated, random number list, flipping coins, randomly picking envelopes, etc. is specified → YES
- If the description only includes "random," "randomly generated," "randomized," etc, do not assume additional details → UNCLEAR
- If the description is quasi-randomized (e.g. alternate randomization, day of the year, day of the month, birth date, birth month, beginning letter of last name, availability of investigator or specialist, etc) → NO

Allocation concealment:

- If the assignment is conducted by central telephone, pharmacy, etc → YES
- If dark (or opaque), sealed, sequentially-numbered envelopes are used → YES
- If the envelopes are not stated to dark and sealed, or sequentially-numbered → UNCLEAR

Note: sequential numbering of the envelopes is only required for adequate allocation concealment if the method of randomization was anything other than randomly picking envelopes (i.e., the envelopes were only used for allocation concealment and not as part of the randomization process).

Blinding:

- Describe who is blinded: patient, clinician, outcomes assessor, etc.
- If the study was stated to be blinded (masked), and the blinding is considered to be possible and not likely to be broken → YES
- If the study is only stated to be blinded, double-blinded, double-dummy, etc. without any further details → UNCLEAR
- If the study states the use of a placebo (dummy), but with no further details → UNCLEAR
- If no mention of blinding → UNCLEAR

Incomplete outcome data (longest time point):

- Look for intention-to-treat (ITT) analysis (all randomized patients are analyzed) → YES
- If all participants were accounted for (i.e., no dropouts or censored analysis conducted) → YES
- If the numbers and reasons for withdrawal or dropouts were described and comparable across groups (and ≤ approximately 10 percent) → YES
- If there is between 10–30 percent dropout and no ITT analysis → UNCLEAR
- If there is greater 30 percent dropout and no ITT analysis → NO

Selective outcome reporting:

- If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they match → YES
- If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they do not match, but there is reference to another publication with this information presented → YES
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they match → YES
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they do not match → NO
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they match but not in an extractable format (e.g., stating that there was no difference between the groups regarding the outcome) → UNCLEAR

Other sources of bias:

- Assess for baseline imbalances that could have biased the results (or were not accounted for)
- Assess for appropriateness of crossover design (e.g., inadequate wash-out period).
- Note any "other" sources of bias

Risk of Bias Assessments

A) Schizophrenia and Related Psychoses

Table 1. Risk of bias–chlorpromazine versus clozapine

Study	Item	Judgment	Description
Chiu et al. 1976[152]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial using identical capsules.
	Incomplete outcome data addressed?	NO	ITT principle was not used in the analyses with 43.8% of participants being excluded from the analyses. Attrition rate was high with 43.8% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Claghorn et al. 1987[63]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial, with medications that were identical in appearance and packaged uniformly.
	Incomplete outcome data addressed?	NO	ITT principle not utilized for analyses, and 42% of participants did not complete the study.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ekblom et al. 1974[153]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB trial using identical capsules.
	Incomplete outcome data addressed?	YES	ITT principle was used and attrition rate was low (9.8%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were reported not reported. Other sources of bias were not detected.

Table 1. Risk of bias–chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description
Gelenberg et al. 1979[154]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding participant or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle was used in analyses with no reports of patients lost for followup.
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Guirguis et al. 1977[160]	Adequate sequence generation?	UNCLEAR	Reported as randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	No mention of who was blinded, but used identical capsules prepared in pharmacy.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 35/50 (70%) analyzed.
	Free of selective reporting?	YES	Protocol not available, but methods and results sections match.
	Free of other bias?	UNCLEAR	Baseline imbalances on age, NOSIE score, and onset of schizophrenia.
Hong et al. 1997[87]	Adequate sequence generation?	YES	Randomization was done using a table of random numbers.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. Medications were identical in appearance and package, which ensured DB. No clear statement regarding blinding of assessors.
	Incomplete outcome data addressed?	YES	No use of ITT. 40 patients randomized, 38 patients analyzed (95%).
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kane et al. 1988[94]	Adequate sequence generation?	UNCLEAR	Reported patients were randomly assigned, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	All medications were coded and administered under DB conditions; in addition to coded active antipsychotic medication in blue capsules, patients received either white benztropine tablets or identical white placebo tablets.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 10–30% (14%) dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 1. Risk of bias–chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description
Leon et al. 1979[156]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	NO	No ITT reported; 50 randomized and 37 analyzed at 3 year followup.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lieberman et al. 2003[109]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial but only specified patients were blinded.
	Incomplete outcome data addressed?	YES	Use of modified ITT. Only 4 patients not considered in the analysis (2.43%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Rinieris et al. 1980[157]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physician blinding status provided in trial report.
	Incomplete outcome data addressed?	NO	ITT principle was not used in analyses, with only 59% of randomized participants included in analyses.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results were similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Shopsin et al. 1979[158]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Blinding?	YES	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses, and there was no reporting of patients dropping out of the trial.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results sections are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were reported not reported. Other sources of bias were not detected.

Table 1. Risk of bias–chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description

Singer et al. 1974[161]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a blinded trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	One dropout from each group.
	Free of selective reporting?	YES	No protocol available, but outcomes in methods and results match.
	Free of other bias?	NO	No mention of baseline comparisons.

DB = double-blind; ITT = intention-to-treat analysis; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 2. Risk of bias–chlorpromazine versus olanzapine

Study	Item	Judgment	Description
Conley et al. 1998[66]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, using matching medication.
	Incomplete outcome data addressed?	UNCLEAR	ITT reported. 70% completion.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 3. Risk of bias–chlorpromazine versus quetiapine

Study	Item	Judgment	Description
Peuskens et al. 1997[121]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT performed on 196/201 (98%) of randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 4. Risk of bias–chlorpromazine versus ziprasidone

Study	Item	Judgment	Description
Kane et al. 2006[96]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis. Response rates and safety evaluations are reported for the ITT population.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 5. Risk of bias–fluphenapine versus olanzapine

Study	Item	Judgment	Description
Jakovljevic et al. 1999[89]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	Modified ITT using LOCF on those who received drug and had at least one followup observation. 55/60 (92%) analyzed for efficacy, 100% for safety.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ljubin et al. 2000[112]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Physicians were blind to patient status, but no report of patients knowledge of treatment received.
	Incomplete outcome data addressed?	UNCLEAR	Only analyzed completers. Due to a dropout of some patients, the final olanzapine group had 10 patients, and the fluphenazine group 8 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis; LOCF = last observation carried forward

Table 6. Risk of bias–fluphenapine versus quetiapine

Study	Item	Judgment	Description
Conley et al. 2005[67]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, but 71% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis;

Table 7. Risk of bias–fluphenapine versus risperidone

Study	Item	Judgment	Description
Conley et al. 2005[67]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, but 71% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 8. Risk of bias–haloperidol versus aripiprazole

Study	Item	Judgment	Description
Andrezina et al. 2006[44]	Adequate sequence generation?	YES	Reported as using permuted block randomization.
	Allocation concealment?	YES	Reported as using a centralized call-in system.
	Blinding?	UNCLEAR	Reported as a DB, placebo-controlled trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis was not used, but 99% of randomized participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Daniel et al. 2007[74]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding seuqence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no futher details regarding blinding.

Table 8. Risk of bias–haloperidol versus aripiprazole (continued)

Study	Item	Judgment	Description
	Incomplete outcome data addressed?	UNCLEAR	Of the 448 patients who received IM formulations, 380 (85%) were transitioned to oral formulations. However, they did not report in this study the results obtained from people switching from placebo to aripiprazole.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
de Oliveira et al. 2009[76]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	Trial reported that investigators were provided with sealed, numbered, and coded envelopes containing the description of the treatment to be administered to the subject by a person who had no contact with the patients. There is no mention if the envelopes were opaque/ dark or not.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT priniciple not used, but 98% of participants included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Kane et al. 2002[92]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding except that rater was blinded to treatment group.
	Incomplete outcome data addressed?	NO	ITT; reported 248/414 completed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	It is unclear if baseline characteristics were similar.
Kasper et al. 2003[98]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as DB, with no further information.
	Incomplete outcome data addressed?	YES	1294 patients randomized, 1289 analyzed; LOCF reported.
	Free of selective reporting?	YES	Methods match results reported.
	Free of other bias?	NO	No significant differences between treatment groups. Study funded by Bristol Myers Squibb.
Kim et al. 2010[102]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a double blind trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 8. Risk of bias–haloperidol versus aripiprazole (continued)

Study	Item	Judgment	Description
McCue et al. 2006[73]	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study, with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Tran-Johnson et al. 2007[31]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used in analyses, but 95% of participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; IM = intramuscular; ITT = intention-to-treat analysis

Table 9. Risk of bias–haloperidol versus asenapine

Study	Item	Judgment	Description
Kane et al. 2010[97]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details.
	Allocation concealment?	UNCLEAR	Allocation concealment was not reported.
	Blinding?	UNCLEAR	Reported as a DB, placebo-controlled trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis was not used, but 98% of randomized participants were included in the analyses.
	Free of selective reporting?	UNCLEAR	InterSePT and RDQ are reported as trial outcomes, but no extractable data is reported (i.e., only reported that changes from baseline to endpoint were small).
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis; RDQ = Readiness to Discharge Questionnaire

Table 10. Risk of bias–haloperidol versus clozapine

Study	Item	Judgment	Description
Breier et al. 2002[56]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, with investigators, raters, clinical staff, and patients blinded by using identical unmarked syringes administered by trained, unblinded, third-party personnel, who played no role in evaluating patients.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses. Attrition rate was low (0.7%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001[62]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Covington et al. 2000[70]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	No reporting of trial blinding.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses and no dropouts were reproted.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Itoh et al. 1977[155]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	Reported that those physicians who had conducted the trial or those who were related to the pharmaceutical company were excluded from the controllers who coded the DB trial and supervised the entire experiment.
	Blinding?	UNCLEAR	Reported that the 'coders' were independent of physcians supervising the trial. So it seems that they were blinded, but no report of the subjects' status.
	Incomplete outcome data addressed?	YES	All patients were analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 10. Risk of bias–haloperidol versus clozapine (continued)

Study	Item	Judgment	Description
Kane et al. 2001[95]	Adequate sequence generation?	YES	Reported as a randomized trial. Computer-generated randomization schedules (blocked by site) were provided to each site.
	Allocation concealment?	UNCLEAR	Use of sealed envelopes with treatment assignment were available to clinical personnel if needed to break the blind. Unsure whether they used sequentially numbered or opaque envelopes.
	Blinding?	UNCLEAR	Reported as a DB trial: medication was administered under DB conditions. To maintain the blind, all subjects had a weekly blood draw. No further details regarding blinding.
	Incomplete outcome data addressed?	NO	More than 30% were droped out of the study, and no ITT was conducted.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kleiser et al. 1994[103]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	51 patients were randomized, 51 analyzed. No report of ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	No significant differences between treatment groups. No declaration of funding source.
Krakowski et al. 2006[105]	Adequate sequence generation?	UNCLEAR	Reported as a block randomization with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all participants.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Rosenheck et al. 1997[126]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial, with matching benztropine placebo. To maintain blinding, haloperidol- treated patients also received benztropine mesylate (2–10 mg/d) for extrapyramidal syndrome; clozapine patients received a matching benztropine placebo. Haloperidol patients participated in weekly blood counts as required for clozapine treatment.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used in analyses and attrition rate was moderate, with 346/423 participants not included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 10. Risk of bias–haloperidol versus clozapine (continued)

Study	Item	Judgment	Description
Volakva et al. 2002[145]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-values, degrees of freedom, and p-values are reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

BDZ = benzodiazepine; DB = double-blind; ESRS =Extrapyramidal Syndrome Rating Scale; ITT = intention-to-treat analysis; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 11. Risk of bias–haloperidol versus olanzapine

Study	Item	Judgment	Description
Altamura et al. 2002[43]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle was not used. 24/28 participants were included in the analyses using LOCF. Attrition rate was moderate (25%).
	Free of selective reporting?	UNCLEAR	Protocol was not available, but one of the main outcomes (CGI–S) was only reported to be not significantly different between the groups, without any extractable data presented.
	Free of other bias?	UNCLEAR	Baseline characteristics for the 2 groups was shown in tabular form, but no mention of similarity was presented.
Alvarez-Jimenez et al. 2006[142]	Adequate sequence generation?	YES	Reported as a randomized trial using computer-generated blocks of random numbers.
	Allocation concealment?	YES	Allocation concealment was done by a member of the team not involved with either the assessment or the treatments.
	Blinding?	NO	Reported as single-blind trial, with research assessors and patients intended to be blind to intervention. It was difficult to keep assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Avasthi et al. 2001[159]	Adequate sequence generation?	YES	Reported as a randomized trial, with no further details regarding sequence generation.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Described as an open-label study.
	Incomplete outcome data addressed?	UNCLEAR	No ITT; 23/30 (76.7%) analyzed.
	Free of selective reporting?	YES	Study protocol not available, but outcomes reported in the methods and results sections match.
	Free of other bias?	UNCLEAR	No baseline comparison data reported.
Beasley et al. 1996[49]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB placebo-controlled trial, with no further details regarding blinding, except that dose ranges could be modified in a blinded manner.
	Incomplete outcome data addressed?	YES	ITT principle not used in the analyses, but 415/431 participants were included using LOCF. Attrition rate was low (16%).
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Beasley et al. 1997[50]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis using LOCF on 415/431 (96%) of patients.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Bernardo et al. 2001[51]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further information regarding blinding.
	Incomplete outcome data addressed?	YES	ITT not used for analyses, with 27/28 participants included. Attrition was not reported.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Boulay et al. 2007[54]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle was not used, with 95% of participants included in analyses. Attrition rate was moderate (12.5%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Breier et al. 2002[56]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, with investigators, raters, clinical staff, and patients blinded by using identical unmarked syringes administered by trained unblinded third-party personnel who played no role in evaluating patients.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses. Attrition rate was low (0.7%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Buchanan et al. 2005[58]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a DB trial, but adverse events were rated by a nonblinded pharmacist.
	Incomplete outcome data addressed?	YES	ITT principle is not used in analyses. Attrition rate was low 9.5%.
	Free of selective reporting?	YES	Protcol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001[62]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high, with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Crespo-Faccoro et al. 2006[71]	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated randomization list.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but attrition rate was low, and 172/182 were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Davidson et al. 2009[75]	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
de Haan et al. 2003[78]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using a randomized block design. No more details regarding sequence generation
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. All analyses were performed blind to the clinical data.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 20% withdrawal.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Goldman et al. 2004[84]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial; no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 7/10 completed.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ishigooka et al. 2001[88]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 127/174 competed the trial.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	UNCLEAR	Significant difference in BPRS scores at baseline. Other sources of bias were not detected.
Kahn et al. 2008[91]	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Keefe et al. 2006[101]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	414 patients randomized. ITT reported. 414 analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kim et al. 2010[102]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kongsakon et al. 2006[104]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	YES	Drug kits were assigned a number according to a randomization list produced onsite, then these numbered kits were consecutively allocated to patients in blocks of four stratified by country.
	Blinding?	YES	Reported as a DB trial. All study medication was identical in appearance.
	Incomplete outcome data addressed?	YES	>90% (93% for PANSS and 98% for BPRS) were analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Krakowski et al. 2006[105]	Adequate sequence generation?	UNCLEAR	Reported as a block randomization with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all participants.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lahti et al. 2009[106]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial. Medications were prepared in similar-looking capsules by the hospital pharmacist.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Incomplete outcome data addressed?	YES	ITT principle not used, but 29/32 (91%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Lieberman et al. 2003[108]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT reported; 263 randomized; 262 analyzed.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lindenmayer et al. 2007[110]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding procedure.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, 31/35 (89%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
McCue et al. 2006[73]	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups, and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Purdon et al. 2000[124]	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated random number table.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	65 randomized, 55 analyzed with LOCF. ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Rosenheck et al. 2003[127]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	YES	Assignments were made from a coordinating center via telephone.
	Blinding?	YES	Reported as a DB trial using kits labelled with a random number; one group received a matching placebo (i.e. both groups took 2 drugs).
	Incomplete outcome data addressed?	YES	ITT analysis on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Saddichha et al. 2008[129]	Adequate sequence generation?	NO	Reported as randomized, but treatment was assigned by order in which patient arrived.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. Assessments conducted by a single-blind investigator. No description of drug appearance to preserve the blinding.
	Incomplete outcome data addressed?	YES	Analyzed 99/110 (90%) enrolled patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.
Sayers et al. 2005[130]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used in analyses; attrition rate was high, with 14/ 24 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Sergi et al. 2007[134]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 73/100 (73%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Smelson et al. 2006[136]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial using identical appearing capsules. No mention of who else blinded.
	Incomplete outcome data addressed?	NO	ITT not reported. 18/31 (58%) included in analysis .
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Smith et al. 2001[137]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT not reported. 53% to 73% included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Tollefson et al. 1997[141]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT analysis on all randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Volakva et al. 2002[145]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-value, degrees of freedom, and p-value are reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Wright et al. 2001[147]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial. Drugs and placebo administered in identical, color-blinded, translucent syringes; raters and study personnel blind to treatment assignment.
	Incomplete outcome data addressed?	YES	ITT not reported but 285/311 (92%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Wynn et al. 2007[148]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Incomplete outcome data addressed?	NO	ITT not reported. 51/100 (51%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

BDZ = benzodiazepine; BPRS = Brief Psychiatric Rating Scale; DB = double-blind; CGI–S = Clinical Global Impressions–Severity; ESRS = Extrapyramidal Symptom Rating Scale; ITT = intention-to-treat analysis; LOCF = last observation carried forward; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale

Table 12. Risk of bias–haloperidol versus quetiapine

Study	Item	Judgment	Description
Arvantis et al. 1997[46]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 99% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Atmaca et al. 2002[47]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	This study was not reported as blinded, and there was not reporting of any blinding.
	Incomplete outcome data addressed?	UNCLEAR	Reported that all participants completed the study.
	Free of selective reporting?	YES	Protocol not available, but outcomes in methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Copolov et al. 2000[68]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no futher details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used and attrition rate was high with 33% of participants dropping out from the trial.
	Free of selective reporting?	YES	Outcomes is the method section match with the results.
	Free of other bias?	UNCLEAR	Baseline characteristics were similar, with the exception for differences in the subgroup diagnoses of schizoprhenia and AIMS scores. Other sources of bias were not detected.
Davidson et al. 2009[75]	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.

Table 12. Risk of bias–haloperidol versus quetiapine (continued)

Study	Item	Judgment	Description
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.

Study	Item	Judgment	Description
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high, with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 2000[79]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	Modified ITT using LOCF on those who received drug and had at least one followup observation. 98% analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 2005[80]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as investigator-blinded trial. No other details about blinding.
	Incomplete outcome data addressed?	YES	47 randomized; 33 analyzed; ITT reported (70% completion).
	Free of selective reporting?	YES	Outcomes in method section are matched to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Glick et al. 2005[65]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition rate was high, with 66% of participants not available at the end of the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kahn et al. 2008[91]	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.

Table 12. Risk of bias–haloperidol versus quetiapine (continued)

Study	Item	Judgment	Description

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
McCue et al. 2006[73]	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Purdon et al. 2001[123]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	Unequal dropout between groups. Analyses included a range of 84% to 100% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected .
Velligan et al. 2002[143]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	This is a substudy analysing 58/116 (50%) of eligible patients and excluded dropouts.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

AIMS = Abnormal Involuntary Movement Scale; DB = double-blind; ITT = intention-to-treat analysis; LOCF = last observation carried forward

Table 13. Risk of bias–haloperidol versus risperidone

Study	Item	Judgment	Description
Apiquain et al. 2008[45]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT priniciple not used during the analysis, and only data from 53% of participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were similar except for educational level, marital status, and occupational status. Other sources of bias were not detected
Blin et al. 1996[52]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle used during analysis, but attrition rate was moderate with 10/ 41 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Borison et al. 1992[53]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT principle was used during analyses. Attrition was not reported to have occurred.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics are presented in tabular format but with no mention of similarity between the groups. Other sources of bias were not detected.
Cavallaro et al. 2001[59]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical tablets.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used in analyses with moderate attrition rate with 22% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Ceskova et al. 1993[60]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physcian blinding status provided in trial report.
	Incomplete outcome data addressed?	YES	ITT principle not used during analyses, but attrition rate was low with 3/62 patients not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Chouinard et al. 1993[61]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical tablets.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses and no reported dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001[62]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no futher details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high, with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Claus et al. 1992[64]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using matched oral solutions of each medication.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 42 (95%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description

Study	Item	Judgment	Description
Crespo-Faccoro et al. 2006[71]	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated randomization list.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but attrition rate was low, and 172/ 182 were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Csernansky et al. 2002[72]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical-appearing tablets.
	Incomplete outcome data addressed?	YES	ITT principle not used in analyses, but the attrition rate was low with 365/397 participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
de Sena et al. 2003[77]	Adequate sequence generation?	NO	Reported that randomization was performed based on the time of inclusion assigning patients to groups to even and odd numbers (i.e., quasi-randomization).
	Allocation concealment?	NO	Allocation concealment was not possible because quasi-randomization was used.
	Blinding?	UNCLEAR	No details regarding patient or physician blinding was provided in the trial report.
	Incomplete outcome data addressed?	UNCLEAR	The number randomized was not provided, and there was no mention of dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 1999[81]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Fakra et al. 2008[82]	Adequate sequence generation?	UNCLEAR	Block randomization with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	UNCLEAR	12% dropout with no ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Heck et al. 2000[85]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis performed on all 77 (100%) patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kee et al. 1998[99]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	20 randomized, 18 analyzed. No ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Keefe et al. 2003[100]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used, 16/49 (33%) of participants included in the analyses, but number per treatment group were not reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Keefe et al. 2006[101]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	414 patients randomized. ITT reported. 414 analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kim et al. 2010[102]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Lee et al. 2007[107]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis included all 20 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lim et al. 2010[151]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial according to a predefined randomization code that was balanced to ensure even distribution of patients in each treatment group.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial, but rater blinded.
	Incomplete outcome data addressed?	YES	ITT & LOCF reported. 124 randomized. 124 analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Liu et al. 2000[111]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using block randomization in sizes of four with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used, 38/56 (68%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Marder et al. 1994[114]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	NO	High attrition rates (53%) due to insufficient response, AEs, uncooperative etc.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Marder et al. 2003[113]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	63 patients randomized, 29 completed the study, 63 patients analyzed. No ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
McCue et al. 2006[73]	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study, with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Min et al. 1993[117]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	All medication was identical and labled with a protocol number.
	Incomplete outcome data addressed?	YES	ITT analysis performed on all 35 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Moller et al. 2008[118]	Adequate sequence generation?	UNCLEAR	Block randomization with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	The ITT sample comprised all randomized patients except those whose initial diagnosis had been revised. 98% were analyzed.
	Free of selective reporting?	YES	Trial design described in a publication prior to results of trial. Methods match results reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Peuskens et al. 1995[120]	Adequate sequence generation?	YES	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	Randomized sequence transferred to sealed envelopes, but did not mention that envelopes were opaque.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT reported. Analysis included 1019/1362 (75%) randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Purdon et al. 2000[124]	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated random number table.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	65 randomized, 55 analyzed with LOCF. ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Remillard et al. 2008[125]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	The experimenter was blind to the participants' medication and psychopathological status; the clinician assessing psychopathology and EPS was blind to their cognitive performance and medication status.
	Incomplete outcome data addressed?	YES	All 28 were included in analyses.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	UNCLEAR	Significant differences in baseline characteristics. Other sources of bias not found.
Schooler et al. 2005[132]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using 1:1 randomization scheme balanced by site, with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	State ITT principle used, but the denominator for primary outcome. They must have analyzed 521/559 (93%) of patients to obtain their result. Over the 2 yrs of trial, there was a 60.4% dropout rate.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Sergi et al. 2007[134]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 73/100 (73%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Shrivastava et al. 2000[135]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as an open-label study.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 100/125 (80%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Tamrakar et al. 2006[139]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a randomized open-label trial.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 36/45 (80%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Volakva et al. 2002[145]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-value, degrees of freedom, and p-value are reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Wirshing et al. 1999[146]	Adequate sequence generation?	YES	Reported as a randomized trial using a computerized random-number-generating program.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	10-30% dropout with no ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Wynn et al. 2007[148]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT not reported. 51/100 (51%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Yen et al. 2004[149]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Single-blind study (rater blinded).
	Incomplete outcome data addressed?	UNCLEAR	Used an endpoint LOCF, but it is not clear if used ITT (41 patients randomized, 14 dropped out) and included all patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

Table 13. Risk of bias–haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Zhang et al. 2001[150]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded assessors. No detail about patient blinding.
	Incomplete outcome data addressed?	YES	ITT not reported but 75/80 (94%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

AE = adverse events; BDZ = benzodiazepine; DB = double-blind; EPS = extrapyramidal symptoms; ESRS = Extrapyramidal Symptom Rating Scale; ITT = intention-to-treat analysis; LOCF = last observation carried forward; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 14. Risk of bias–haloperidol versus ziprasidone

Study	Item	Judgment	Description
Brook et al. 2005[57]	Adequate sequence generation?	UNCLEAR	Reported as randomized trial using a 3:1 randomization ratio, with no further details in the trial report.
	Allocation concealment?	UNCLEAR	Reported as masked randomization schedule consisting of a list of numbers to which the study drugs had been randomly allocated, but there were no details on how the masking was performed.
	Blinding?	NO	Reported that this trial was an open-label, flexible-dose design trial, with all assessments conducted by evaluators blinded to drug allocation.
	Incomplete outcome data addressed?	NO	ITT principle was used with LOCF method used for missing data, but there was a high attrition rate with 33% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are consistent.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Corripio et al. 2005[69]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	NO	Reported as a single-blined trial, with physicians blinded to treatment status and patients not blinded.
	Incomplete outcome data addressed?	YES	ITT principle used with no reported dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Davidson et al. 2009[75]	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Goff et al. 1998[83]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT reported. Unknown number screened or randomized, 46/90 completed.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 14. Risk of bias–haloperidol versus ziprasidone (continued)

Study	Item	Judgment	Description

Study	Item	Judgment	Description
Hirsch et al. 2002[86]	Adequate sequence generation?	NO	Reported using a computer-generated pseudo-random code.
	Allocation concealment?	UNCLEAR	Reported use of 'envelope method,' but no further details provided.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 227/301 (75%) analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kahn et al. 2008[91]	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
McCue et al. 2006[73]	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the six treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Miceli et al. 2010[116]	Adequate sequence generation?	YES	Reported as a randomized trial: patients were randomly assigned, using a computer-generated protocol.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a single blind trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	59 patients randomized to treatment. 9 patients discontinued treatment (15.25%). Not reported use of ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

Table 14. Risk of bias–haloperidol versus ziprasidone (continued)

Study	Item	Judgment	Description

Study	Item	Judgment	Description
Potkin et al. 2009[122]	Adequate sequence generation?	YES	Randomization was by computer-generated schedule with a permuted block design.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	No ITT. The full analysis set included 536 subjects who had at least one post-baseline efficacy assessment. 536/599 (89%) analyzed at end of 40 week phase using LOCF, and 186/186 analyzed after 3 year extension using LOCF (Table 2.)
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat; LOCF = last observation carried forward

Table 15. Risk of Bias – perphenazine versus aripiprazole

Study	Item	Judgment	Description
Kane et al. 2007[93]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	Modified ITT. Included only subjects who took 1 dose of medication (LOCF); 75% completed the 6 weeks treatment (25% dropouts).
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	UNCLEAR	It is unclear if baseline characteristics were similar.

DB = double-blind; ITT = intention-to-treat; LOCF = last observation carried forward

Table 16. Risk of bias–perphenazine versus olanzapine

Study	Item	Judgment	Description
Ascher-Svanum et al. 2008[131]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label treatment.
	Incomplete outcome data addressed?	YES	664 patients randomized. 648 analyzed. No ITT reported.
	Free of selective reporting?	YES	Methods match results reported.
	Free of other bias?	YES	No significant differences between treatment groups.
Lieberman et al. 2005[23]	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 17. Risk of bias–perphenazine versus quetiapine

Study	Item	Judgment	Description
Lieberman et al. 2005[23]	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: Patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 18. Risk of bias–perphenazine versus risperidone

Study	Item	Judgment	Description
Ascher-Svanum et al. 2008[131]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label treatment.
	Incomplete outcome data addressed?	YES	664 patients randomized. 648 analyzed. No ITT reported.
	Free of selective reporting?	YES	Methods match results reported.
	Free of other bias?	YES	No significant differences between treatment groups.
Lieberman et al. 2005[23]	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 19. Risk of bias–perphenazine versus ziprasidone

Study	Item	Judgment	Description
Lieberman et al. 2005[23]	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 20. Risk of bias– trifluoperazine versus clozapine

Study	Item	Judgment	Description
Rinieris et al. 1980[157]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physcian blinding status.
	Incomplete outcome data addressed?	NO	ITT principle was not used in analyses with only 59% of randomized participants included in analyses.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results were similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

DB = double-blind; ITT = intention-to-treat

B) Bipolar Disorder

Table 21. Risk of bias–chlorpromazine versus clozapine

Study	Item	Judgment	Description
Barbini et al. 1997[48]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 90% of randomized participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Treatment groups were similar except duration of last euthymic period, which was significantly longer in participants randomized to chlorpromazine. Other sources of bias were not detected.

ITT = intention-to-treat

Table 22. Risk of bias – haloperidol versus aripiprazole

Study	Item	Judgment	Description
Vieta et al. 2005[32]	Adequate sequence generation?	UNCLEAR	Reported as using a fixed randomization schedule, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 338/ 347 participants were included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Young et al. 2009[33]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physcian blinding status provided in trial report.
	Incomplete outcome data addressed?	YES	ITT principle not used and attrition rate was high with 43% of randomized participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 23. Risk of bias–haloperidol versus olanzapine

Study	Item	Judgment	Description
Moreno et al. 2007[119]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial. The two drugs to be compared had the same appearance and were packaged identically, and matched in order to satisfy the requirements of a DB study.
	Incomplete outcome data addressed?	YES	All 12 patients included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Patients did have statistically significant differences between groups. Other sources of bias were not detected.
Tohen et al. 2003[140]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial. Not clear how the sequence was generated.
	Allocation concealment?	YES	Allocation concealment was done using a call-in interactive voice response system.
	Blinding?	UNCLEAR	Blinding was not reported.
	Incomplete outcome data addressed?	NO	ITT reported 256/453 completed.
	Free of selective reporting?	YES	All outcomes in methods are apparently reported in results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 24. Risk of bias–haloperidol versus quetiapine

Study	Item	Judgment	Description
McIntyre et al. 2005[115]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; medication was identical in number, form, and color but no mention of assessor blinding.
	Incomplete outcome data addressed?	YES	ITT performed on 299/302 randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 25. Risk of bias–haloperidol versus risperidone

Study	Item	Judgment	Description
Janicak et al. 2001[90]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Described as DB using identical-appearing preparations supplied by Janssen Pharmaceutical Products.
	Incomplete outcome data addressed?	NO	Results tables have no Ns reported, but Table 1 indicates that 25/62 (40%) finished the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Sachs et al. 2002[128]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used in analyses and attrition rate was high with 59/ 105 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Segal et al. 1998[133]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Smulevich et al. 2005[138]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT not reported but 297/297 (100%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 26. Risk of bias–haloperidol versus ziprasidone

Study	Item	Judgment	Description
Vieta et al. 2010[144]	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in the trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB, double-dummy, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT priniciple used in the analyses, but the attrition rate was high with 57% of participants did not complete the trial.
	Free of selective reporting?	YES	Protocol not available, but the outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Appendix F. Summary Risk of Bias Assessments

Table 27. Study-level distribution

	Number of studies
Low risk of bias	0 (0%)
Unclear risk of bias	79 (64%)
High risk of bias	44 (36%)

Table 28. Domain-level distribution

Domain	High	Unclear	Low
Adequate sequence generation	3 (2.4%)	105 (85.4%)	15 (12.2%)
Allocation concealment	1 (0.8%)	116 (94.3%)	6 (4.9%)
Blinding	21 (17.1%)	83 (67.5%)	19 (15.4%)
Incomplete outcome data addressed	24 (19.5%)	32 (26.0%)	67 (54.5%)
Free of selective reporting	1 (0.8%)	3 (2.4%)	119 (96.7%)
Free of other bias	0 (0.0%)	20 (16.3%)	103 (83.7%)

Appendix G. Newcastle-Ottawa Scale Assessment of Cohort Studies

Table 29. Quality assessment of cohort studies

					Selection		Compara-bility		Outcome	
Author, year	**Study design**	**Repre-sentative-ness of cohort**	**Selection of non-exposed cohort**	**Ascertain-ment of exposure**	**Outcome of interest**	**Compara-bility of cohorts**	**Assess-ment of outcome**	**Adequate duration of followup**	**Adequate follow-up of cohort**	**Total score**
Gaszner 2004[162]	Retrospective cohort study	A (1*)	A (1*)	A (1*)	A (1*)	A (1*)	B (1*)	A (1*)	A (1*)	8
Hennessy 2002[163]	Retrospective cohort study	A (1*)	A (1*)	A (1*)	A (1*)	A (1*)	B (1*)	A (1*)	A (1*)	8

Appendix H. General Study Characteristics

A) Schizophrenia and Related Psychoses

Table 30. Patient characteristics–chlorpromazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Chiu et al. 1976[152]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Australia ***Financial support:*** Industry (Sandoz) ***Washout period performed:*** yes (5d) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (<60 yrs) with acute episodes of Sz (moderate to severe symptomatology); not suffering from any major medical illnesses ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 30.00±NR ***Males (n(%)):*** 4/14 (28.57%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 32.60±NR ***Males (n(%)):*** 12/22 (54.55%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–300mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 50–300mg/d ***Intervals:*** NR
Claghorn et al. 1987[63]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM II ***Study period:*** NR ***Number of centers:*** Multicenter (n = 6) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** yes (2 wks) ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts (18–65 yrs) with Sz (DSM–II); good physical health, exhibited neurological reactions (either tardive dyskinesia or extrapyramidal effects) induced by prior medication with at least two different AP; hospitalization under 6 months; BPRS score of at least 4 ***Main exclusion criteria:*** Pts with medical disorders that could alter the metabolism of the test agents; sensitivities to AP; organic mental disease, recent Hx of ECT; pregnancy	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 54.94±14.24 ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 58.05±14.64	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50mg–1800mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 25mg–900mg/d ***Intervals:*** NR

Table 30. Patient characteristics–chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ekblom et al. 1974[153]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Sweden ***Financial support:*** NR ***Washout period performed:*** yes (2 wks) ***Run-in phase performed:*** no ***Followup period:*** 5.71 wks	***Main inclusion criteria:*** Male acute Sz, and relapsed or exacerbated chronic Sz cases of the paranoid/hallucinatory or catatonic type ***Main exclusion criteria:*** Pt age (over sixty or under fifteen); pts suffering from certain previously defined other illness, such as hypertonia, liver disease, etc	***G1:*** ***Age (mean±SD):*** 28.00±NR ***Males (n(%)):*** 21/21 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 33.00±NR ***Males (n(%)):*** 20/20 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 65–700mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 65–600mg/d
Gelenberg et al. 1979[154]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM II ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Sandoz) ***Washout period performed:*** yes (48 h) ***Run-in phase performed:*** no ***Followup period:*** 4–8 wks	***Main inclusion criteria:*** Pts (18–65 yrs) with Sz (DSM–II); BPRS rating of at least moderate on at least 3 of the items; Hx of neurologic reaction associated with previous antipsychotic drug use; suitability for treatment with oral medication; good physical health ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 30.80±NR ***Males (n(%)):*** 4/8 (50%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 47±NR ***G2:*** ***Age (mean±SD):*** 28.30±NR ***Males (n(%)):*** 4/7 (57.14%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 45±NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–1800mg/d ***Intervals:*** TID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 25–900mg/d ***Intervals:*** TID
Guirguis et al. 1977[160]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Canada ***Financial support:*** NR ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 7 wks	***Main inclusion criteria:*** Dx with acute Sz; previously untreated acute Sz, acutely relapsed Sz and acute exacerbations in chronic Sz ***Main exclusion criteria:*** Severe somatic illnesses; drug allergies; pathological changes in blood picture; Hx of Parkinsonism, epilepsy or problems in micturition; disturbance in consciousness; glaucoma; pregnant	***G1:*** ***Age (mean±SD):***34.7±2.0 ***Males (n(%)):*** 20/28 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 41.5±2.5 ***Males (n(%)):*** 15/22 (68.1%) ***Ethnicity:*** NR ***BL symptom scores:***NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 150–900mg/d ***Intervals:*** TID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 75–450mg/d ***Intervals:*** TID

Table 30. Patient characteristics–chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hong et al. 1997[87]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1995 to NA ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** China ***Financial support:*** Academic ***Washout period performed:*** NA ***Run-in phase performed:*** yes (6 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Sz pt, treatment refractory, Hx of symptoms for 6 months, no less than 2 on BPRS ***Main exclusion criteria:*** Pt with: Hx drug abuse, alcoholism, organic brain disorder, mental retardation, or condition that contraindicates clozapine	***G1:*** ***Age (mean±SD):*** 37.10±8.70 ***Males (n(%)):*** 7/19 (36.84%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 53.1±9.1 PANSS (mean±SD): 113±22 ***G2:*** ***Age (mean±SD):*** 39.70±8.40 ***Males (n(%)):*** 7/21 (33.33%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 52.7±6.9 PANSS (mean±SD): 109±18	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–1800mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 25–900mg/d
Kane et al. 1988[94]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM III ***Study period:*** NR ***Number of centers:*** Multicenter (n = 16) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry ***Washout period performed:*** NA ***Run-in phase performed:*** ***Drug:*** yes (6 wks) ***Followup period:*** 6 wks	***Main inclusion criteria:*** total BPRS score at least 45 and a minimum CGI rating of 4; item scores of at least (moderate) were required on 2 of the items: conceptual disorganization, suspiciousness, hallucination behavior, and unusual thought content; Hx of Tx resistance; Tx refractory Sz Pts; 3 periods of Tx in the last 5 yrs w/neuroleptics from 2 different chemical classes; doses equivalent to 1000mg/d chlorpromazine for 6 wks without relief and no period of functioning within the preceding 5 yrs ***Main exclusion criteria***: NR	***G1:*** ***Age (mean±SD):*** 35.70±8.87 ***Males (n(%)):*** 114/142 (80.28%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 61±11 ***G2:*** ***Age (mean±SD):*** 35.70±8.87 ***Males (n(%)):*** 101/126 (80.16%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 61±12	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 1000–1800mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 500–900mg/d ***Intervals:*** NR

Table 30. Patient characteristics–chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Leon et al. 1979[156]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** WHO 1973 / APA ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Outpatient ***Country:*** Columbia ***Financial support:*** Industry (Sandoz) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 208 wks	***Main inclusion criteria:*** Sz pts ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 27.30±NR ***Males (n(%)):***15/25 (60%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.5±9.3 ***G2:*** ***Age (mean±SD):*** 30.00±NR ***Males (n(%)):*** 14/25 (56%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 40.5±10	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 100–1600mg/d ***Intervals:*** TID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 100–1600mg/d ***Intervals:*** TID
Lieberman et al. 2003[109]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Oct 1995 to Dec 1998 ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** China ***Financial support:*** Industry (Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Dx of Sz or schizophreniform disorder; duration of symptoms not longer than 60 mo; no prior Tx with antipsychotic medication or, if previously treated, a total lifetime usage of less than 14 d; between 16–40 yrs of age; current psychotic symptoms of moderate severity or greater measured by one of the five psychotic items in the (BPRS). ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 28.70±6.90 ***Males (n(%)):*** 42/80 (52.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 44.4±NR ***G2:*** ***Age (mean±SD):*** 28.70±6.90 ***Males (n(%)):*** 42/80 (52.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.3±NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** max of 600mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** max of 400mg/d

Table 30. Patient characteristics–chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rinieris et al. 1980[157]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Greece ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 6 wks	***Main inclusion criteria:*** Sz pts with absence of clinical symptoms; no Hx of thyroid or endocrinological disease; no use of psychotropic meds ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.5±9.3 ***G2:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 40.5±10 ***G3:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 36.4±11.4	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–100mg ***Intervals:*** TID ***G2:*** ***Classification:*** FGA ***Drug:*** Trifluoperazine ***Dosage:*** 2.5–5mg ***Intervals:*** TID ***G3:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 50–100mg ***Intervals:*** TID
Shopsin et al. 1979[158]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** yes (≥1 wks) ***Run-in phase performed:*** NR ***Followup period:*** 5 wks	***Main inclusion criteria:*** Chronically ill Pts with Sz with a recent Hx of acute exacerbation necessitating involuntary hospitalization; those showing minimal criteria under disturbances of affect, thought, and behavior included ***Main exclusion criteria:*** Acute or chronic brain syndromes; alcohol/drug addiction; epilepsy; pregnancy; unwillingness to participate in the study; unmanageable ward behavior; refusal to take oral medications; medicolegal difficulties; spontaneous remission during the baseline placebo period	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–1600mg/d ***Intervals:*** TID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 25–900mg/d ***Intervals:*** TID

Table 30. Patient characteristics–chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Singer et al. 1974[161]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Hong Kong ***Financial support:*** NR ***Washout period performed:*** Yes (2wks) ***Run-in phase performed:*** no ***Followup period:*** 40 days	***Main inclusion criteria:*** Dx with acute Sz; ***Main exclusion criteria:*** Pts with severe somatic illnesses (hepatic, renal and cardiovascular disturbances including compensated and decompensated cardiac diseases, hypotension and, hypertension); drug allergies, histories of epileptic seizures and severe disturbances of consciousness, possibility of pregnancy or pregnant; closed angle glaucoma.	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–600mg/d ***Intervals:*** QID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 0–600mg/d ***Intervals:*** QID

AP = antipsychotic; APA = American Psychiatric Association; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECT = electroconvulsive therapy; FGA = first-generation antipsychotic; Hx = history; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; pts = patients; QID = Four times daily; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; Tx = treatment; WHO = World Health Organization; wk = week; yr = year

Table 31. Patient characteristics–chlorpromazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 1998[66]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly) ***Washout period performed:*** yes (NA) ***Run-in phase performed:*** yes (6 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Pts with Sz (DSM–III–R) with Tx resistance; ≥ 2 periods of Tx in preceding 5 yrs with AP (from at ≥2 chemical classes, excluding haloperidol), at dosages ≥1000mg/d of chlorpromazine equivalents, for 6 wks without significant symptomatic relief; no period of good functioning within past 5 yrs; BPRS (total) score ≥45; CGI–S score ≥4 on at least two of the BPRS psychosis items ***Main exclusion criteria:*** resistance to clozapine	***G1:*** ***Age (mean±SD):*** 42.63±10.89 ***Males (n(%)):*** 28/42 (66.7%) ***Ethnicity:*** Caucasian 29/42 (69.1%) ***BL symptom scores:*** BPRS (mean±SD): 55.1±8.3 ***G2:*** ***Age (mean±SD):*** 42.91±8.57 ***Males (n(%)):*** 34/42 (81%) ***Ethnicity:*** Caucasian 28/42 (66.7%) ***BL symptom scores:*** BPRS (mean±SD): 55.5±7.8	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 600–1200mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 12.5–25mg/d ***Intervals:*** BID

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 32. Patient characteristics–chlorpromazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Peuskens et al. 1997[121]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 28) ***Setting:*** Inpatient ***Country:*** Belgium, UK, Spain, France, South Africa ***Financial support:*** Industry (Zeneca) ***Washout period performed:*** yes (24 h) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Age 18–65; acute exacerbation of chronic or subchronic Sz, or schizophreniform disorder; BPRS score = 27; BPRS pos score = 3 on two or more of 'conceptual disorganization', 'suspiciousness', 'hallucinatory behavior' and 'unusual thought content'; a score of = 4 on CGI–S. ***Main exclusion criteria:*** Any medical condition or laboratory abnormality that might confound the trial results; had received long–acting depot medication; had participated in another investigational drug trial during the 4 wks prior to randomization; evidence of significant alcohol or other drug abuse within the previous 12 mo.	***G1:*** ***Age (mean±SD):*** 34.00±11.00 ***Males (n(%)):*** *66*/100 (66%) ***Ethnicity:*** Caucasian 80/100(80%) ***BL symptom scores:*** BPRS (mean±SD): 44±11 PANSS (mean±SD): 27.8±8 ***G2:*** ***Age (mean±SD):*** 32.00±10.00 ***Males (n(%)):*** 63/101 (62.4%) ***Ethnicity:*** Caucasian 81/101 (80.2%) ***BL symptom scores:*** BPRS (mean±SD): 46±10 PANSS (mean±SD): 28±8	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 75–750mg/d ***Intervals:*** TID ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 75–750mg/d ***Intervals:*** TID

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; Tx = treatment; wk = week; yr = year

Table 33. Patient characteristics–chlorpromazine versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2006[96]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 8) ***Setting:*** Outpatient ***Country:*** India ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (6 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Men and Women ≥18yrs with chronic or subchronic Sz; Tx resistant; Haloperidol nonresponders; total score ≥45 on the BPRS; a score ≥4 on at least two PANSS core psychosis items (conceptual disorganization, hallucinatory behavior, delusions and suspiciousness); and a score ≥4 on the CGI–S scale. ***Main exclusion criteria:*** Respond to haloperidol during run in phase	***G1:*** ***Age (mean±SD):*** 34.40±8.20 ***Males (n(%)):***122/154 (79.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 50.54±NR ***G2:*** ***Age (mean±SD):*** 35.60±9.50 ***Males (n(%)):***103/152 (67.8%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 50.47±NR	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 100–1200mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** BID

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; NA = not applicable; n = number; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 34. Patient Characteristics–fluphenazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Jakovljevic et al. 1999[89]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Inpatient ***Country:*** Croatia ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (1 to 1.5 wks) ***Run-in phase performed:*** no ***Followup period:*** 22 wks	***Main inclusion criteria:*** Age 18–65 yrs; Dx with Sz; BPRS score≥42; CGI–S score≥4; PANSS≥42 ***Main exclusion criteria:*** Hx of unstable illness, intolerance to Olanzapine or Fluphenazine, substance dependence, abnormal liver function, hepatitis, jaundice. Tx with depot neuroleptics; suicidal ideation, pregnant or lactating, previous trial with olanzapine.	***G1:*** ***Age (mean±SD):*** 36.00±9.80 ***Males (n(%)):*** 14/30 (46.7%) ***Ethnicity:*** Caucasian 30/30 (100%) ***BL symptom scores:*** BPRS (mean±SD): 42.7±10.3 PANSS (mean±SD): 106.9±18.5 ***G2:*** ***Age (mean±SD):*** 34.80±11.10 ***Males (n(%)):*** 14/30 (46.7%) ***Ethnicity:*** Caucasian 81/101 (100%) ***BL symptom scores:*** BPRS (mean±SD): 43.7±8.7 PANSS (mean±SD): 110.5±16.4	***G1:*** ***Classification:*** FGA ***Drug:*** Fluphenazine ***Dosage:*** 6–21mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 34. Patient Characteristics–fluphenazine versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ljubin et al. 2000[112]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Outpatient ***Country:*** Croatia ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (2–9 d) ***Followup period:*** 22 wks	***Main inclusion criteria:*** Outpatients Dx with Sz and CGI–S score = 4; females must be using a medically accepted means of contraception; must have a level of understanding to communicate intelligently with the investigators and nurses; must be reliable and understand the nature of the study ***Main exclusion criteria:*** Dx of DSM–IV organic mental disorder or substance use disorder within past 3 mo.; serious suicidal risk; pregnant or lactating; serious unstable co–morbid condition; life expectancy = 3yrs; exposure to olanzapine or fluoxetine = 4 wks, remoxipride = 6 mo; Tx with non–reversible monoamine oxidase inhibitor = 2 wks; lithium, anticonvulsants, benzodiazepines, antidepressants, psychostimulants, reversible monoamine oxidase inhibitor, reserpine, guanethidine, or guanadrel = 1 wk.	***G1:*** ***Age (mean±SD):*** 37.00±NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 37.00±NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Fluphenazine ***Dosage:*** 6–21mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 35. Patient characteristics–fluphenazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 2005[67]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (4–6 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Age 18–65yrs; Dx with Sz; medically healthy, considered treatment resistant; persistent positive psychotic symptoms (≥4 points on 2 of 4 psychosis items on BPRS); BPRS≥ 45 pts; CGI–S ≥4; 2 failed Tx trials with 2 different APs; no stable period of good social/ occupational functioning within the previous 5 yrs; non response to run-in Tx. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 44.20±8.8 ***Males (n(%)):*** 11/13 (84.6%) ***Ethnicity:*** Caucasian 7/13 (53.9%) ***BL symptom scores:*** BPRS (mean±SD): 54.69±13.67 ***G2:*** ***Age (mean±SD):*** 43.70±5.90 ***Males (n(%)):*** 10/12 (83.3%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 53.5±7.37 ***G3:*** ***Age (mean±SD):*** 46.30±8.70 ***Males (n(%)):*** 9/13 (69.2%) ***Ethnicity:*** Caucasian 7/13 (53.9%) ***BL symptom scores:*** BPRS (mean±SD): 56±14.08	***G1:*** ***Classification:*** FGA ***Drug:*** Fluphenazine ***Dosage:*** 10–15mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 300–500mg/d ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 3–5mg/d

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; WHO = World Health Organization; wk = week; yr = year

Table 36. Patient characteristics–fluphenazine versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 2005[67]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (4–6 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Age 18–65yrs; Dx with Sz; medically healthy, considered treatment resistant; persistent positive psychotic symptoms (≥4 points on 2 of 4 psychosis items on BPRS); BPRS≥ 45 pts; CGI–S ≥4; 2 failed Tx trials with 2 different APs; no stable period of good social/ occupational functioning within the previous 5 yrs; non response to run-in Tx. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 44.20±8.80 ***Males (n(%)):*** 11/13 (84.6%) ***Ethnicity:*** Caucasian 7/13 (53.9%) ***BL symptom scores:*** BPRS (mean±SD): 54.69±13.67 ***G2:*** ***Age (mean±SD):*** 43.70±5.90 ***Males (n(%)):*** 10/12 (83.3%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 53.5±7.37 ***G3:*** ***Age (mean±SD):*** 46.30±8.70 ***Males (n(%)):*** 9/13 (69.2%) ***Ethnicity:*** Caucasian 7/13 (53.9%) ***BL symptom scores:*** BPRS (mean±SD): 56±14.08	***G1:*** ***Classification:*** FGA ***Drug:*** Fluphenazine ***Dosage:*** 10–15mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 300–500mg/d ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 3–5mg/d

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 37. Patient characteristics–haloperidol versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Andrezina et al. 2006[44]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Dec 2003 to Jun 2004 ***Number of centers:*** Multicenter (n = 68) ***Setting:*** Inpatient ***Country:*** USA, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain ***Financial support:*** Industry (Bristol–Myers Squibb, Otsuka) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 24h	***Main inclusion criteria:*** Pts (18 yrs or older) experiencing acute agitation and Dx of Sz or schizoaffective disorder (DSM–IV); PEC scores >15 and <32; score of >4 on at least two of the five PEC items. ***Main exclusion criteria:*** Dx of schizophreniform disorder or other psychiatric Dx; Pts with significant risk of suicide; clinically significant neurologic diagnoses; Hx of seizures; Hx of abnormal EEG, severe head trauma, or stroke or evidence of other unstable medical conditions; substance or alcohol dependence within 2 months before the study; suspected substance–induced psychiatric disorder or behavioral disturbance; Hx of neuroleptic malignant syndrome from antipsychotic agents; use of benzodiazepines or anticholinergics within 4 h before the first injection of study medication; and lack of response to previous antipsychotic medication	***G1:*** ***Age (mean±SD):*** 41.80±NR ***Males (n(%)):*** 59/185 (31.89%) ***Ethnicity:*** Caucasian 61/185 (33%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 41.90±NR ***Males (n(%)):*** 63/175 (36%) ***Ethnicity:*** Caucasian 70/175 (40%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 6.5mg ***Intervals:*** every 2 hrs (max 3/d) ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 9.75mg ***Intervals:*** every 2 hrs (max 3/d)

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Daniel et al. 2007[74]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Bristol–Myers Squibb) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 5 d	***Main inclusion criteria:*** Acutely agitated Pts (18–69 yrs) with Sz or schizoaffective disorder (DSM–IV) and confirmed by the MINI; PEC = 15 –32, greater than 4 on at least 2 PEC items ***Main exclusion criteria:*** Pts with Axis I (DSM–IV) Dx of schizophreniform disorder, Dx other than Sz or schizoaffective disorder requiring pharmacotherapy or suicidal; Hx of seizure or other neurologic disorders or abnormal EEG or other significant medical Hx; substance dependence/abuse; clinically significant lab value or baseline ECG findings; Hx of hypersensitivity to AP; need or potential need for St. John's Wort, carbamazepine, rifampicin, phenytoin, or ECT or use 2 wks prior to the trial; use of benzodiazepines within 4 hrs prior to the study; nonresponse to previous AP; need for restraints; pregnant/lactating women	***G1:*** ***Age (mean±SD):*** 41.80±NR ***Males (n(%)):*** 110/185 (59.5%) ***Ethnicity:*** Caucasian 113/185 (61.1%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 41.90±NR ***Males (n(%)):*** 110/ 175 (62.9%) ***Ethnicity:*** Caucasian122/175 (69.7%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 6.5mg/d ***Intervals:*** max 3 inj every 2 hrs ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 9.75mg/d ***Intervals:*** max 3 inj every 2 hrs

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
de Oliveira et al. 2009[76]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jul–03 to Mar–05 ***Number of centers:*** Multicenter (n = 10) ***Setting:*** Outpatient ***Country:*** Brazil ***Financial support:*** Industry (Bristol–Myers Squibb) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts (18–65 yrs) with Sz or schizoaffective disorder (DSM–IV–TR); PANSS (total) score >60 ***Main exclusion criteria:*** Clinically significant organic or neurologic disorders; epilepsy; psychiatric disorders other than Sz and schizoaffective disorder; Hx of alcohol/drug abuse in the previous 3 months; participated in trials using investigational drugs over the last 12 months; pregnant/nursing mothers and those of childbearing potential without adequate contraceptive methods	***G1:*** ***Age (mean±SD):*** 34.20±9.70 ***Males (n(%)):*** 21/33 (63.6%) ***Ethnicity:*** Caucasian 15/33 (45.5%) ***BL symptom scores:*** CGI-BP (mean±SD): 4.7±0.75 PANSS (mean±SD): 85.1±14.9 ***G2:*** ***Age (mean±SD):*** 34.50±13.20 ***Males (n(%)):*** 33/ 66 (50%) ***Ethnicity:*** Caucasian 37/66 (56.1%) ***BL symptom scores:*** CGI-BP (mean±SD): 4.85±0.92 PANSS (mean±SD): 87.7±15.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–15mg/d ***Intervals:*** Once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15–30mg/d ***Intervals:*** Once daily

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2002[92]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jul–97 to Jun–98 ***Number of centers:*** Multicenter (n = 36) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Bristol–Myers Squibb and Otsuka) ***Washout period performed:*** yes (<1 wks) ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Age (18–65) Dx Sz, or Sz–affective according to DSM–IV; not refractory to antipsychotics, had improvement with agents besides clozapine; outpatient for at least one 3–month period in last yr ***Main exclusion criteria:*** Psychotic disorder other than schizophrenia or schizoaffective disorder, Hx of violence, suicidal attempts, serious suicidal ideation, a clinically significant neurologic abnormality other than tardive dyskinesia or EPS, drug abuse or dependence. Tx with investigational drug in last month.	***G1:*** ***Age (mean±SD):*** 38.90±9.18 ***Males (n(%)):*** 68/104 (65.4%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 99.3±17.34 ***G2:*** ***Age (mean±SD):*** 37.80±10.10 ***Males (n(%)):*** 76/102 (74.5%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 98.5±17.17 ***G3:*** ***Age (mean±SD):*** 39.30±10.10 ***Males (n(%)):*** 70/102 (68.6%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 99±19.19	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15mg/d ***Intervals:*** once daily ***G3:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 30mg/d ***Intervals:*** once daily

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kasper et al. 2003[98]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 133) ***Setting:*** NR ***Country:*** Austria ***Financial support:*** Bristol–Myers Squibb ***Washout period performed:*** yes (5 days) ***Run-in phase performed:*** no ***Followup period:*** 52 wks	***Main inclusion criteria:*** Experiencing an acute relapse; Hx of previous response to antipsychotic medication (other than clozapine) and not considered refractory to typical antipsychotic medication ***Main exclusion criteria:*** initial episode of schizophrenia, currently or recently (<1 month)	***G1:*** ***Age (mean±SD):*** 36.80±0.40 ***Males (n(%)):***247/433 (57.0%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 36.80±0.50 ***Males (n(%)):*** 511/861 (59.3%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–10mg ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 20–30mg ***Intervals:*** once daily

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010[102]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** *Two–center* ***Setting:*** Outpatient ***Country:*** South Korea ***Financial support:*** Other (Choi Shine ***Hae 2008–2009)*** ***Washout period performed:*** yes (>4wks) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Patients with schizophrenia, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all participants were smokers; clinically stable, with no changes in their antipsychotic medication prescriptions ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 42.50±8.70 ***Males (n(%)):*** 25/35 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 37.10±4.80 ***Males (n(%)):*** 23/31 (74.2%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 41.80±11.40 ***Males (n(%)):*** 23/32 (71.9%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 39.90±12.80 ***Males (n(%)):*** 28/41 (68.3%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15.9+/-7.1mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 21.7+/-5.5 mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15.9+/-4.3mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4.8+/-2.9mg/d ***Intervals:*** NR

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006[73]	***Study design:*** Randomized controlled trial ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan 2004 to Feb 2005 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Trial characteristics:*** ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Pts (>=18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder ***Main exclusion criteria:*** Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder	***G1:*** ***Age (mean±SD):*** 37.50±10.80 ***Males (n(%)):*** 42/57 (73.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42±11.3 ***G2:*** ***Age (mean±SD):*** 40.50±12.60 ***Males (n(%)):***27/ 53 (51.0%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.3±10.2	***G1:*** ***Classification:*** FGA ***Intervention:*** Haloperidol ***Dosage:*** 4-30mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Intervention:*** Aripiprazole ***Dosage:*** 10-45mg ***Intervals:*** NR

Table 37. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tran-Johnson et al. 2007[31]	***Study design:*** RCT ***Registration #:*** NCT00036127 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Apr–02 to Jan–03 ***Number of centers:*** Multicenter (n = 50) ***Setting:*** NR ***Country:*** USA and 20 others ***Financial support:*** Industry (Bristol–Meyers Squibb Co., Otsuka Inc) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 24 h	***Main inclusion criteria:*** Symptoms of acute agitation; Dx with Sz, schizoaffective disorder, or schizophreniform disorder; PANSS–PEC score 15 and 32; moderate score on 2/5 PEC items; 18 yrs; appropriate for IM Tx for acute agitation ***Main exclusion criteria:*** Pts who had psychoactive substance dependence within 2 months of study start; required involuntary restraint; were suicidal; had a neurologic or psychiatric condition other than Sz, schizoaffective disorder, or schizophreniform disorder; had a significant medical condition; were known nonresponders to antipsychotic medication	***G1:*** ***Age (mean±SD):*** 40.85±10.16 ***Males (n(%)):*** 39/60 (65%) ***Ethnicity:*** Caucasian 43/60 (71.7%) ***BL symptom scores:*** BPRS (mean±SD): 58.93±NR ***G2:*** ***Age (mean±SD):*** 41.46±10.12 ***Males (n(%)):*** 37/57 (64.9%) ***Ethnicity:*** Caucasian 39/57 (68.4%) ***BL symptom scores:*** BPRS (mean±SD): 57.79±NR ***G3:*** ***Age (mean±SD):*** 39.46±10.19 ***Males (n(%)):*** 35/63 (55.6%) ***Ethnicity:*** Caucasian 47/63 (74.6%) ***BL symptom scores:*** BPRS (mean±SD): 57.03±NR ***G4:*** ***Age (mean±SD):*** 41.18±10.88 ***Males (n(%)):*** 36/57 (63.2%) ***Ethnicity:*** Caucasian 41/57 (71.9%) ***BL symptom scores:*** BPRS (mean±SD): 58.66±NR ***G5:*** ***Age (mean±SD):***	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 7.5mg/d ***Intervals:*** 2–20 hrs ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 1mg/d ***Intervals:*** 2–20 hrs ***G3:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 5.25mg/d ***Intervals:*** 2–20 hrs ***G4:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 9.75mg/d ***Intervals:*** 2–20 hrs ***G5:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15mg/d ***Intervals:*** 2–20 hrs

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			44.24±9.96 ***Males (n(%)):***35/ 58 (60.3%) ***Ethnicity:*** Caucasian 40/58 (69%) ***BL symptom scores:*** BPRS (mean±SD): 58.16±NR	

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; ECG = Electrocardiography; ECT = Electroconvulsive therapy; EEG = Electroencephalography; EPS = Extrapyramidal symptoms; FGA = first-generation antipsychotic; hr = hour; inj = injection; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PEC = Positive excitement component; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 38. Patient characteristics–haloperidol versus asenapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2010[97]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jun 2005 to Sep 2006 ***Number of centers:*** Multicenter (n = 43) ***Setting:*** Mixed ***Country:*** USA, Canada, Russia, India, Romania, Croatia ***Financial support:*** Industry (Schering–Plough) ***Washout period performed:*** yes (1–3d) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** At least 18 Yrs; DSM–IV Sz with acute exacerbation of psychotic symptoms; PANSS score ≥60; scores ≥ 4 on 2 of 5 predefined PANSS pos subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution); CGI–S score ≥4. ***Main exclusion criteria:*** Clinically significant medical condition or abnormal laboratory or physical examination findings; Dx of residual–type Sz, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; current or past substance abuse; 20% or higher decrease in PANSS total score from screening to baseline; known allergy or sensitivity to haloperidol; imminent risk of self–harm or harm to others; and previous participation in an asenapine trial.	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):***NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** NR ***Males (n(%)):***NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Asenapine ***Dosage:*** 5mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Asenapine ***Dosage:*** 10mg/d ***Intervals:*** BID

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 39. Patient characteristics–haloperidol versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Breier et al. 1994[55]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Government ***Washout period performed:*** NA ***Run-in phase performed:*** yes (6 wks) ***Followup period:*** 10 wks	***Main inclusion criteria:*** Pts (18–55 yrs) chronic Sz (DSM–III–R) who had not responded to a 6–week trial of fluphenazine ***Main exclusion criteria:*** Concurrent drug/alcohol abuse, organic brain disorders, mental retardation, or a medical condition that contraindicates clozapine use	***G1:*** ***Age (mean±SD):*** 35.00±8.00 ***Males (n(%)):*** 15/20 (75%) ***Ethnicity:*** Caucasian 14/20 (70%) ***BL symptom scores:*** BPRS (mean±SD): 38.1±8.2 ***G2:*** ***Age (mean±SD):*** 34.00±6.00 ***Males (n(%)):*** 13/19 (68.4%) ***Ethnicity:*** Caucasian 15/19 (79%) ***BL symptom scores:*** BPRS (mean±SD): 36.7±10.6	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–600mg/d ***Intervals:*** NR

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001[62]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1996 to 2000 ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 14 wks	***Main inclusion criteria:*** Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs ***Main exclusion criteria:*** Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 31/37 (83.8%) ***Ethnicity:*** Caucasian 11/37 (29.7%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 34/40 (85%) ***Ethnicity:*** Caucasian 12/40 (30%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 33/39 (84.6%) ***Ethnicity:*** Caucasian 12/39 (30.8%) ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 35/41 (85.4%) ***Ethnicity:*** Caucasian 13/41 (31.7%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** NR

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Covington et al. 2000[70]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Unclear ***Country:*** USA ***Financial support:*** Government ***Washout period performed:*** yes (NA) ***Run-in phase performed:*** no ***Followup period:*** 24 mo	***Main inclusion criteria:*** Pts with Sz or schizoaffective disorder (DSM–III–R) ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 24.10±5.05 ***Males (n(%)):*** 34/42 (81%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 25.30±5.65 ***Males (n(%)):*** 27/40 (67.5%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** NR ***Intervals:*** NR
Gaszner et al. 2004[162]	***Study design:*** Retrospective cohort study ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–IV–TR ***Study period:*** 1980 to 2002 ***Number of centers:*** Single center ***Setting:*** NR ***Country:*** Hungary ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 22 yrs	***Main inclusion criteria:*** Pts with Sz (DSM–IV–TR); Clozapine Tx ≥1 yr ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 43.10±4.00 ***Males (n(%)):*** 55/152(36.1%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 42.40±7.44 ***Males (n(%)):*** 72/181 (39.8%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1.5–4.5mg/d ***Intervals:*** Once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 50–200mg/d ***Intervals:*** Once daily

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hennessy et al. 2002[163]	***Study design:*** Retrospective cohort study ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** 1993 to 1996 ***Number of centers:*** Multicenter ***Setting:*** outpatient ***Country:*** USA ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** Until end of prescription duration	***Main inclusion criteria:*** Individuals with more >1 prescription for oral thioridazine, haloperidol, risperidone, or clozapine plus at least 2 instances of a Sz Dx ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):***NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** NR ***Intervals:*** NR
Itoh et al. 1977[155]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Multicenter (n = 7) ***Setting:*** Inpatient ***Country:*** Japan ***Financial support:*** Unclear (NR) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** Sz pts ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):***NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.25–15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 75–500mg/d ***Intervals:*** NR

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2001[95]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Multiple sources (Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** yes ***Followup period:*** 29 wks	***Main inclusion criteria:*** DSM–III–R Dx of Sz or schizoaffective disorder, 20–55 yrs of age, and living in the community or judged clinically treatable in the community; partial or poor response was defined by documented treatment failure in 2 trials of conventional antipsychotics at dosages equivalent to or greater than chlorpromazine hydrochloride, 600mg/d, for at least 6 wks (high–dose qualification) and 1 trial of a conventional agent at dosages equivalent to chlorpromazine hydrochloride, 250–500mg/d, for the same length of time (low–dose qualification). ***Main exclusion criteria:*** Use psychotropic medication therapy other than antipsychotics (eg, antidepressants or mood stabilizers) that could not be discontinued, documented Hx of intolerance to haloperidol at dosages of 4mg/d or more because of disabling extrapyramidal adverse effects, Dx of neuroleptic malignant syndrome with recurrence on rechallenge, evidence that refractoriness was related to medication noncompliance, organic brain disease (eg, epilepsy or brain tumor), mental retardation that precluded understanding study participation or assessment procedures, chronic medical illness that made study participation inappropriate, DSM–III–R diagnosis of substance abuse or dependence within 6 months, current treatment with medication(s) for other medical	***G1:*** ***Age (mean±SD):*** 40.00±8.00 ***Males (n(%)):*** 24/34 (70.6%) ***Ethnicity:*** Caucasian 24/34 (70.6%) ***BL symptom scores:*** BPRS (mean±SD): 44.7±9.3 ***G2:*** ***Age (mean±SD):*** 41.00±10.00 ***Males (n(%)):*** 26/37 (70.3%) ***Ethnicity:*** Caucasian 25/37 (67.6%) ***BL symptom scores:*** BPRS (mean±SD): 47.4±10.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–16mg/d ***Interval:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 12.5–800mg/d ***Interval:*** NR

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
		conditions that may have psychotropic effects or agranulocytosis risk or may interfere with drug absorption or metabolism, total white blood cell count below 3.5_103/μL (3500/mm^3), and pregnancy		
Kleiser et al. 1994[103]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM III ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Unclear ***Country:*** Germany ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Pts who had not received any neuroleptic pretreatment suffering from an acute Sz paranoid type (ICD–9 295.3) ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 33.70±9.70 ***Males (n(%)):*** 7/17 (41.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 55±12 ***G2:*** ***Age (mean±SD):*** 31.10±11.10 ***Males (n(%)):*** 6/17 (35.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 58±10	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 16mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 350mg/d ***Intervals:*** NR ***Dosage:*** 10–35mg/d

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Krakowski et al. 2006[105]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jun 1999 to Nov 2004 ***Number of centers:*** Multicenter (n = 2) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1–2 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Aged 18–60 yrs and Dx with Sz or schizoaffective disorder using diagnostic criteria DSM–IV; patients were required to have a clearly confirmed episode of physical assault directed at another person during this hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property. ***Main exclusion criteria:*** Hospitalized for more than a yr; if they had a Hx of nonresponse to clozapine, olanzapine, or haloperidol; if they had a history of clozapine, olanzapine, or haloperidol intolerance; or if they had medical conditions that would be adversely affected by any of these 3 medications; received a depot antipsychotic within 30 d before randomization	***G1:*** ***Age (mean±SD):*** 32.70±10.60 ***Males (n(%)):*** 30/36 (83.3%) ***Ethnicity:*** Caucasian 7/36 (19.4%) ***BL symptom scores:*** PANSS (mean±SD): 85.5±13.2 ***G2:*** ***Age (mean±SD):*** 35.10±12.30 ***Males (n(%)):*** 31/37 (83.8%) ***Ethnicity:*** Caucasian 7/37 (18.9%) ***BL symptom scores:*** PANSS (mean±SD): 86.4±14.4 ***G3:*** ***Age (mean±SD):*** 35.60±9.40 ***Males (n(%)):*** 29/37 (78.4%) ***Ethnicity:*** Caucasian 5/37 (13.5%) ***BL symptom scores:*** PANSS (mean±SD): 83.7±14.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Interval:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Interval:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:***10-35mg/d ***Interval:*** NR

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rosenheck et al. 1997[126]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** Mar 1993 to Apr 1995 ***Number of centers:*** Multicenter (n = 15) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Sandoz) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** The study targeted Pts with Sz refractory to Tx and a Hx of a high level of use of inpatient services, defined as 30 to 364 d of hospitalization for schizophrenia during the previous yr; clinical eligibility criteria consisted of a Dx of Sz, as defined in the (DSM–IIIR) ***Main exclusion criteria:*** Unable to give informed consent, had been treated previously with clozapine, had a current myeloproliferative disorder, pregnant	***G1:*** ***Age (mean±SD):*** 43.90±8.30 ***Males (n(%)):*** 211/218 (96.8%) ***Ethnicity:*** Caucasian 145/218 (66.5%) ***BL symptom scores:*** PANSS (mean±SD): 92.2±14.5 ***G2:*** ***Age (mean±SD):*** 43.20±7.70 ***Males (n(%)):*** 202/205 (98.5%) ***Ethnicity:*** Caucasian 135/205 (65.9) ***BL symptom scores:*** PANSS (mean±SD): 91±14.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5 to 30mg/d ***Interval:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 100 to 900mg/d ***Interval:*** NR

Table 39. Patient characteristics–haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002[145]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** June 1996 to NR ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 14 wks	***Main inclusion criteria:*** Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs, defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS ***Main exclusion criteria:*** A Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 90.4±11.6 ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 97.6±17.1 ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 91±13.5 ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 89.5±13.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** BID

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 40. Patient characteristics–haloperidol versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Altamura et al. 2002[43]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** NR ***Country:*** Italy ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 14 wks	***Main inclusion criteria:*** Dx of paranoid Sz who showed partial response to neuroleptics after ≥6wks of doses of different classes. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 38.30±8.00 ***Males (n(%)):*** 7/11 (63.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 50.5±14.4 ***G2:*** ***Age (mean±SD):*** 39.30±12.40 ***Males (n(%)):*** 6/13 (46.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 61.4±15	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–20mg/d ***Intervals:*** NR
Alvarez–Jimenez et al. 2006[142]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** Spain ***Financial support:*** Foundation ***Washout period performed:*** yes (3–5 d) ***Run-in phase performed:*** no ***Followup period:*** 3 mo	***Main inclusion criteria:*** aged 15–60 yrs; DSM–IV criteria for Sz, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief reactive psychosis, or psychosis not otherwise specified; lived in the catchment area; and provided written informed consent; pts were experiencing their first episode of psychosis and had not received more than 6 wks of adequate neuroleptic Tx ***Main exclusion criteria:*** A Hx of neurologic disease, head injury, mental retardation (DSM–IV criteria), or drug dependence (DSM–IV criteria)	***G1:*** ***Age (mean±SD):*** 26.80±7.70 ***Males (n(%)):*** 46/61 (75.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 26.80±7.70 ***Males (n(%)):*** 46/61 (75.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 26.80±7.70 ***Males (n(%)):*** 46/61 (75.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3 to 9mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 3–6mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Avasthi et al. 2001[159]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** India ***Financial support:*** Industry (Eli Lily) ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 3 mo	***Main inclusion criteria:*** Male or female aged 18–65 yrs; Dx with Sz; CGI–S score≥3 ***Main exclusion criteria:*** Positive for hepatitis surface antigen (HBs Ag), IgM fraction of the hepatitis core antibody (anti–HBc[IgMD or had jaundice, current agranulocytosis (absolute neutrophil count <500 mm3)	***G1:*** ***Age (mean±SD):*** NR ***Males (n(%)):***NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 25.00±4.56 ***G2:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 23.31±9.94	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5 to 20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Beasley et al. 1996[49]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** 1991 to 1993 ***Number of centers:*** Multicenter (n = 22) ***Setting:*** Mixed ***Country:*** USA, Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (variable depending on medication) ***Run-in phase performed:*** yes (≤1 wk) ***Followup period:*** 1 yr	***Main inclusion criteria:*** Pts with Sz with acute exacerbation; BPRS score at least 24 ***Main exclusion criteria:*** Organic mental disorders; substance abuse: suicidal risk: unstable mental illnesses: Parkinson disease: myasthenia gravis: illness contraindicating use of anticholinergics: Hx of seizures, leukopenia or abnormal liver function; placebo responders	***G1:*** ***Age (mean±SD):*** 36.00±9.00 ***Males (n(%)):*** 62/69 (89.9%) ***Ethnicity:*** Caucasian 40/69 (58%) ***BL symptom scores:*** BPRS (mean±SD): 41.8±11.4 ***G2:*** ***Age (mean±SD):*** 36.00±9.00 ***Males (n(%)):*** 60/65 (92.3%) ***Ethnicity:*** Caucasian 42/65 (64.6%) ***BL symptom scores:*** BPRS (mean±SD): 41.2±11.7 ***G3:*** ***Age (mean±SD):*** 36.00±9.00 ***Males (n(%)):*** 56/64 (87.5%) ***Ethnicity:*** Caucasian 46/64 (71.9%) ***BL symptom scores:*** BPRS (mean±SD): 42.8±10 ***G4:*** ***Age (mean±SD):*** 36.00±9.00 ***Males (n(%)):*** 54/69 (78.3%) ***Ethnicity:*** Caucasian 54/69 (78.3%) ***BL symptom scores:*** BPRS (mean±SD): 42.6±10.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 2.5–7.5mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5–12.5mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 12.5–17.5mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Beasley et al. 1997[50]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** Nov–91 to Nov–93 ***Number of centers:*** Multicenter (n = 50) ***Setting:*** Inpatient ***Country:*** Europe, South Africa, Israel, Australia ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (≥2d for oral and ≥2wks for depot APs) ***Run-in phase performed:*** yes (4–7d) ***Followup period:*** 1 yr	***Main inclusion criteria:*** Age 18–65 yrs; Dx with Sz and an acute exacerbation; BPRS total score ≥ 24; CGI_S ≥4 (moderate) ***Main exclusion criteria:*** DSM–III–R organic mental disorder or substance use disorder in last 3 mo.; at risk of suicide; had Parkinson's disease, myasthenia gravis, or unstable medical illness that contraindicated the use of anticholinergics; Hx of seizures or leukopenia; elevated liver function tests, active hepatitis B, or jaundice; placebo responder during run-in phase	***G1:*** ***Age (mean±SD):*** 36.00±10.00 ***Males (n(%)):*** 48/81 (59.3%) ***Ethnicity:*** Caucasian 66/81 (81.5%) ***BL symptom scores:*** BPRS (mean±SD): 41.2±10.7 PANSS (mean±SD): 105.3±18.5 ***G2:*** ***Age (mean±SD):*** 34.00±10.00 ***Males (n(%)):*** 58/88 (65.9%) ***Ethnicity:*** Caucasian 77/88 (87.5%) ***BL symptom scores:*** BPRS (mean±SD): 39.5±10.3 PANSS (mean±SD): 100.9±17.9 ***G3:*** ***Age (mean±SD):*** 34.00±12.00 ***Males (n(%)):*** 57/87 (65.5%) ***Ethnicity:*** Caucasian 75/87 (86.2%) ***BL symptom scores:*** BPRS (mean±SD): 40.1±11.2 PANSS (mean±SD): 102.7±19.4 ***G4:*** ***Age (mean±SD):*** 36.00±11.00 ***Males (n(%)):*** 55/86 (64%) ***Ethnicity:*** Caucasian 74/86 (86.1%)	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15±5mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 1.0mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5±2.5mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10±2.5mg/d ***Intervals:*** NR ***G5:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15±2.5mg/d ***Intervals:*** NR

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			BL symptom scores: BPRS (mean±SD): 40.4±9.5 PANSS (mean±SD): 102.2±16.9 ***G5:*** ***Age (mean±SD):*** 36.00±11.00 ***Males (n(%)):*** 57/89 (64%) ***Ethnicity:*** Caucasian 80/89 (90%) ***BL symptom scores:*** BPRS (mean±SD): 42.3±10.9 PANSS (mean±SD): 105.6±18.9	

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Bernardo et al. 2001[51]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Spain ***Financial support:*** Industry (Lilly SA) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Pts with Sz/schizophreniform disorder (DSM–IV) with acute psychosis ***Main exclusion criteria:*** Significant organic disorders; substance abuse; resistance to antipsychotics; treatment with depot neuroleptics in last 6 mo	***G1:*** ***Age (mean±SD):*** 29.90±9.80 ***Males (n(%)):*** 10/13 (76.9%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 52.7±13.3 PANSS (mean±SD): 96.1±25.5 ***G2:*** ***Age (mean±SD):*** 26.90±5.40 ***Males (n(%)):*** 7/14 (50%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 55.5±11.5 PANSS (mean±SD): 101.3±21	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10mg/d ***Intervals:*** NR
Boulay et al. 2007[54]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Mixed ***Country:*** Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (0.43 wks) ***Run-in phase performed:*** no ***Followup period:*** 56 d	***Main inclusion criteria:*** Pts within 5 yrs of Sz Dx (DSM–IV); were in a medication transition phase; PANSS (total) between 60–100 ***Main exclusion criteria:*** Hx of seizure disorder, traumatic brain injury resulting in loss of consciousness; current alcohol/drug abuse; received depot neuroleptic treatment within past 6 months; developmentally delayed	***G1:*** ***Age (mean±SD):*** 34.73±10.62 ***Males (n(%)):*** 8/11 (72.7%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 72.38±13.76 ***G2:*** ***Age (mean±SD):*** 32.86±12.08 ***Males (n(%)):*** 10/14 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 76.14±10.07	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 2.5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Breier et al. 2002[56]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 14) ***Setting:*** Inpatient ***Country:*** Croatia, Italy, Romania, South Africa ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (2–24 hrs) ***Run-in phase performed:*** no ***Followup period:*** 24 hrs	***Main inclusion criteria:*** Recently hospitalized pts (18 yrs and older); Dx of Sz, schizophreniform disorder, schizoaffective disorder; PANSS–EC score at least 14 with at least 4 on at least 1 item; acutely agitated and required parenteral AP Tx ***Main exclusion criteria:*** Significant medical disorders, including alcohol/drug dependency, unable to give consent and cooperate	***G1:*** ***Age (mean±SD):*** 37.40±10.60 ***Males (n(%)):*** 22/40 (55%) ***Ethnicity:*** Caucasian 25/40 (62.5%) ***BL symptom scores:*** PANSS (mean±SD): 19.3±3.1 ***G2:*** ***Age (mean±SD):*** 36.20±10.50 ***Males (n(%)):*** 31/48 (64.6%) ***Ethnicity:*** Caucasian 29/48 (60.42) ***BL symptom scores:*** PANSS (mean±SD): 18.3±2.4 ***G3:*** ***Age (mean±SD):*** 35.10±10.10 ***Males (n(%)):*** 27/45 (60%) ***Ethnicity:*** Caucasian 31/45 (68.9%) ***BL symptom scores:*** PANSS (mean±SD): 19.7±3.4 ***G4:*** ***Age (mean±SD):*** 35.90±11.30 ***Males (n(%)):*** 26/46 (56.5%) ***Ethnicity:*** Caucasian 29/46 (63%) ***BL symptom scores:*** PANSS (mean±SD): 18.9±2.6 ***G5:*** ***Age (mean±SD):***	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 7.5mg ***Intervals:*** max 3 doses/d (every 2–4 hrs) ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 2.5mg ***Intervals:*** max 3 doses/d (every 2–4 hrs) ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5.0mg ***Intervals:*** max 3 doses/d (every 2–4 hrs) ***G4:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5mg ***Intervals:*** max 3 doses/d (every 2–4 hrs) ***G5:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10mg ***Intervals:*** max 3 doses/d (every 2–4 hrs)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			36.70±12.10 ***Males (n(%)):*** 26/46 (56.5%) ***Ethnicity:*** Caucasian 32/46 (69.6%) ***BL symptom scores:*** PANSS (mean±SD): 19.3±2.6	

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Buchanan et al. 2005[58]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (4 wks) ***Followup period:*** 16 wks	***Main inclusion criteria:*** Pts with Sz/schizoaffective disorder with partial response to conventional APs; BPRS (positive) score at least 8 or score of at least 4 on any single item ***Main exclusion criteria:*** Concurrent drug/alcohol abuse; organic brain disorders/mental retardation; demonstrated at least 30% improvement on fluphenazine, relapsed or were intolerant of fluphenazine during run-in	***G1:*** ***Age (mean±SD):*** 46.40±9.00 ***Males (n(%)):*** 24/34 (70.6%) ***Ethnicity:*** Caucasian 16/34 (47.1%) ***BL symptom scores:*** BPRS (mean±SD): 34.7±8.8 ***G2:*** ***Age (mean±SD):*** 41.90±7.00 ***Males (n(%)):*** 22/29 (75.9%) ***Ethnicity:*** Caucasian 18/29 (62.1%) ***BL symptom scores:*** BPRS (mean±SD): 35.5±9.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–30mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001[62]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1996 to 2000 ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 14 wks	***Main inclusion criteria:*** Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs ***Main exclusion criteria:*** Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 31/37 (83.8%) ***Ethnicity:*** Caucasian 11/37 (29.7%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 34/40 (85%) ***Ethnicity:*** Caucasian 12/40 (30%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 33/39 (84.6%) ***Ethnicity:*** Caucasian 12/39 (30.8%) ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 35/41 (85.4%) ***Ethnicity:*** Caucasian 13/41 (31.7%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Crespo–Facorro et al. 2006[71]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Feb–01 to Feb–05 ***Number of centers:*** Single center ***Setting:*** Mixed ***Country:*** Spain ***Financial support:*** Multiple sources (NR) ***Washout period performed:*** yes (3–5d) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (15–60 yrs) with Sz (DSM–IV); no AP within 6 wks; SAPS of moderate severity ***Main exclusion criteria:*** Mental retardation; drug dependence	***G1:*** ***Age (mean±SD):*** 28.30±8.70 ***Males (n(%)):*** 36/56 (64.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 62.4±10.9 YMRS (mean±SD): 9.3±4.3 ***G2:*** ***Age (mean±SD):*** 27.50±6.90 ***Males (n(%)):*** 33/55 (60%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 59.9±12.1 YMRS (mean±SD): 9.2±4.7 ***G3:*** ***Age (mean±SD):*** 26.10±7.60 ***Males (n(%)):*** 38/61 (62.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 56.8±10.3 YMRS (mean±SD): 8.8±4.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–9mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 3–6mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009[75]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 50) ***Setting:*** NR ***Country:*** 13 European countries and Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 mo	***Main inclusion criteria:*** recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 26.03±5.80 ***Males (n(%)):*** 32/52 (61.5%) ***Ethnicity:*** Caucasian 48/52 (92.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.35±19.4 ***G2:*** ***Age (mean±SD):*** 26.18±5.20 ***Males (n(%)):*** 40/60 (66.7%) ***Ethnicity:*** Caucasian 59/60 (98.3%) ***BL symptom scores:*** PANSS (mean±SD): 90.08±21.7 ***G3:*** ***Age (mean±SD):*** 26.07±5.60 ***Males (n(%)):*** 42/74 (56.8%) ***Ethnicity:*** Caucasian 70/74 (94.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.8±21.4 ***G4:*** ***Age (mean±SD):*** 25.56±5.90 ***Males (n(%)):*** 21/45 (46.7%) ***Ethnicity:*** Caucasian 43/45 (95.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.76±19.5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
de Haan et al. 2003[78]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Mixed ***Country:*** Netherlands ***Financial support:*** Government ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (17–28 yrs) with Sz (DSM–IV) ***Main exclusion criteria:*** Neurological or endocrine disease, mental retardation, the use of adjunctive medications such as mood stabilizers or antidepressants; Hx of Tx with clozapine; Hx of unresponsiveness to haloperidol or olanzapine; IM AP within the last yr	***G1:*** ***Age (mean±SD):*** 21.00±2.79 ***Males (n(%)):*** 12/12 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 21.00±2.33 ***Males (n(%)):*** 11/12 (91.7%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.5mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5mg/d ***Intervals:*** once daily
Goldman et al. 2004[84]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts with Sz or schizoaffective disorder (DSM–IV); polyuria in absence of recognized factors ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 41.00±14.70 ***Males (n(%)):*** 4/5 (80%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 86.6±22 ***G2:*** ***Age (mean±SD):*** 35.40±4.40 ***Males (n(%)):*** 5/5 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 79±31.4	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** 5–mg increments ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** 5–mg increments

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ishigooka et al. 2001[88]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** ICD–1O DCR ***Study period:*** NR ***Number of centers:*** Multicenter (n = 67) ***Setting:*** Mixed ***Country:*** Japan ***Financial support:*** NR ***Washout period performed:*** yes (2–4 wks) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Men and women between the ages of 18–65 yrs; met the F.20 category in the ICD–10 DCR classification ***Main exclusion criteria:*** Tx with Haloperidol, Olanzapine or other investigational drug in last 3 months, contraindicated to study medications, Hx liver, kidney, heart disease; pregnant or nursing; neuroleptic malignant syndrome; leukopenia or granulocytopenia; Parkinson's; abnormal transaminase; jaundice	***G1:*** ***Age (mean±SD):*** 42.90±NR ***Males (n(%)):*** 56/89 (62.9%) ***Ethnicity:*** Caucasian 0/89 (0%) ***BL symptom scores:*** BPRS (mean±SD): 45.5±11.7 PANSS (mean±SD): 83.5±21.2 ***G2:*** ***Age (mean±SD):*** 42.90±NR ***Males (n(%)):*** 58/93 (62.4%) ***Ethnicity:*** Caucasian 0/93 (0%) ***BL symptom scores:*** BPRS (mean±SD): 47.9±12.2 PANSS (mean±SD): 88.3±21.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–12mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–15mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008[91]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Dec 2002 to Jan 2006 ***Number of centers:*** Multicenter (n = 50) ***Setting:*** Mixed ***Country:*** European countries, Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, Sanofi–Aventis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI ***Main exclusion criteria:*** More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts	***G1:*** ***Age (mean±SD):*** 25.40±5.60 ***Males (n(%)):*** 64/103 (62.1%) ***Ethnicity:*** Caucasian 93/103 (90.3%) ***BL symptom scores:*** PANSS (mean±SD): 88.9±19.8 ***G2:*** ***Age (mean±SD):*** 26.30±5.90 ***Males (n(%)):*** 67/105 (63.8%) ***Ethnicity:*** Caucasian 100/105(95.2%) ***BL symptom scores:*** PANSS (mean±SD): 87.5±21.1 ***G3:*** ***Age (mean±SD):*** 26.40±5.70 ***Males (n(%)):*** 68/104 (65.4%) ***Ethnicity:*** Caucasian 97/104 (93.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.5±22.6 ***G4:*** ***Age (mean±SD):*** 26.70±5.70 ***Males (n(%)):*** 41/82 (50%) ***Ethnicity:*** Caucasian 77/82 (93.9%) ***BL symptom scores:*** PANSS (mean±SD): 88.3±20.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–16mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2006[101]	***Study design:*** RCT ***Registration #:*** F1D–MC–HGGN ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** July 1999–Nov 2000 to July 1999–Nov 2001 ***Number of centers:*** Multicenter (n = 39) ***Setting:*** Mixed ***Country:*** USA, Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 52 wks	***Main inclusion criteria:*** 18–55yrs; Sz or schizoaffective disorder; PANSS score ≥ 4 on at least 2 positive items; BPRS score ≥18; English speaking; have a level of understanding sufficient to agree to all tests and examinations; had illness duration of at least 2 yrs from first hospitalization and/or diagnosis/treatment; female patients of childbearing potential must have been using a medically accepted means of contraception ***Main exclusion criteria:*** Previous participation in present study, participated in a clinical trial of another investigational drug within 1 mo.; participated in a study within the past 3 mo. that included the neurocognitive battery; significant neurological disorder, head injury with loss of consciousness; serious illness such that death was anticipated within 1 yr or intensive care hospitalization was anticipated within 6 mo, QTc interval greater than 450 ms, uncorrected hypo– or hyperthyroidism, current agranulocytosis, female patients who were either pregnant or nursing, allergic reaction to study medication, DSM–IV substance dependence) within past 2 mo, Tx with depot antipsychotics, reversible MAO inhibitor within 2 wks, or clozapine or ECT within 1 mo	***G1:*** ***Age (mean±SD):*** 39.80±8.32 ***Males (n(%)):*** 69/97 (71.1%) ***Ethnicity:*** Caucasian 51/97 (52.6%) ***BL symptom scores:*** MADRS (mean±SD): 14.4±10.2 PANSS (mean±SD): 82.7±14.1 ***G2:*** ***Age (mean±SD):*** 38.40±7.90 ***Males (n(%)):*** 115/159 (72.3%) ***Ethnicity:*** Caucasian 95/159 (59.8%) ***BL symptom scores:*** MADRS (mean±SD): 13.2±8.7 PANSS (mean±SD): 82.6±13.1 ***G3:*** ***Age (mean±SD):*** 39.50±8.25 ***Males (n(%)):*** 111/158 (70.3%) ***Ethnicity:*** Caucasian 101/158 (63.9%) ***BL symptom scores:*** MADRS (mean±SD): 14.1±9.3 PANSS (mean±SD): 84.1±14.7	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–19mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–10mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010[102]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** *Two–center* ***Setting:*** Outpatient ***Country:*** South Korea ***Financial support:*** Other (Choi Shine Hae 2008–2009) ***Washout period performed:*** yes (>4wks) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts with Sz, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all pts were smokers; they were clinically stable, with no changes in their antipsychotic medication prescriptions. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 42.50±8.70 ***Males (n(%)):*** 25/35 (71.43%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 37.10±4.80 ***Males (n(%)):*** 23/31 (74.2%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 41.80±11.40 ***Males (n(%)):*** 23/32 (71.9%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 39.90±12.80 ***Males (n(%)):*** 28/41 (68.3%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15.9+/-7.1mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 21.7+/-5.5 mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15.9+/-4.3mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4.8+/-2.9mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kongsakon et al. 2006[104]	***Study design:*** RCT ***Registration #:*** F1D–SN–S010 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 22) ***Setting:*** Outpatient ***Country:*** Philippines, Pakistan, Malaysia, Thailand, and Singapore ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (2–9d) ***Run-in phase performed:*** no ***Followup period:*** 24 wks	***Main inclusion criteria:*** outpatients aged between 18–65 yrs, DSM–IV diagnostic criteria for Sz; a BPRS total score of > 18, patients and their caregivers to be reliable and in possession of a sufficient level of understanding to achieve compliance with the protocol; female patients on contraception. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 31.80±10.00 ***Males (n(%)):*** 83/132 (62.9%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.85±17.32 PANSS (mean±SD): 104.85±30.2 ***G2:*** ***Age (mean±SD):*** 32.70±10.00 ***Males (n(%)):*** 73/144 (50.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.45±16.58 PANSS (mean±SD): 104.19±28.15	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20 mg ***Intervals:*** 5 mg increments with 7 d between successive increases ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20 mg ***Intervals:*** 5 mg increments with 7 d between successive increases

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Krakowski et al. 2006[105]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jun 1999 to Nov 2004 ***Number of centers:*** Multicenter (n = 2) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1–2 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Aged 18–60 yrs and Dx with Sz or schizoaffective disorder using diagnostic criteria DSM–IV; Pts were required to have a clearly confirmed episode of physical assault directed at another person during this hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property ***Main exclusion criteria:*** Hospitalized for more than a yr; Hx of nonresponse to clozapine, olanzapine, or haloperidol; Hx of clozapine, olanzapine, or haloperidol intolerance; or if they had medical conditions that would be adversely affected by any of these 3 medications; received a depot antipsychotic within 30 d before randomization	***G1:*** ***Age (mean±SD):*** 32.70±10.60 ***Males (n(%)):*** 30/36 (83.3%) ***Ethnicity:*** Caucasian 7/36 (19.4%) ***BL symptom scores:*** PANSS (mean±SD): 85.5±13.2 ***G2:*** ***Age (mean±SD):*** 35.10±12.30 ***Males (n(%)):*** 31/37 (83.8%) ***Ethnicity:*** Caucasian 7/37 (18.9%) ***BL symptom scores:*** PANSS (mean±SD): 86.4±14.4 ***G3:*** ***Age (mean±SD):*** 35.60±9.40 ***Males (n(%)):*** 29/37 (78.4%) ***Ethnicity:*** Caucasian 5/37 (13.5%) ***BL symptom scores:*** PANSS (mean±SD): 83.7±14.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–35mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lahti et al. 2009[106]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Government ***Washout period performed:*** yes (2 wks) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Medically healthy individuals with Sz on the basis of the clinical interview and all other sources of data using DSM IV criteria ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 38.30±12.20 ***Males (n(%)):*** 10/12 (83.3%) ***Ethnicity:*** Caucasian 5/12 (41.7%) ***BL symptom scores:*** BPRS (mean±SD): 34.4±7.6 ***G2:*** ***Age (mean±SD):*** 36.10±10.50 ***Males (n(%)):*** 12/17 (70.6%) ***Ethnicity:*** Caucasian 3/17 (17.7%) ***BL symptom scores:*** BPRS (mean±SD): 37.3±8.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 12.5–25mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2003[108]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 14) ***Setting:*** Mixed ***Country***: north America, Western Europe ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (≤2wks) ***Run-in phase performed:*** no ***Followup period:*** 104 wks	***Main inclusion criteria:*** ages 16–40 yrs; had onset of psychotic symptoms before age 35 yrs; DSM–IV diagnostic criteria for Sz, schizophreniform disorder, or schizoaffective disorder; research experienced psychotic symptoms (delusions, hallucinations, thought disorder, and grossly bizarre behavior) for at least 1 month but not more than 60 months, 5); scored =4 on at least two PANSS (24) psychosis items (P1, P2, P3, P5, or P6) or scored =5 on one psychosis item; 6) had a (CGI) severity score =4 (moderately ill); 7) required treatment with antipsychotic drugs on a clinical basis ***Main exclusion criteria:*** Previous AP drug Tx≥ 16 wks.; clozapine Tx at anytime; injectable depot neuroleptic within < three dosing intervals before study entry; pregnant or nursing; serious, unstable medical illnesses or findings that contraindicate AP drug Tx; Hx of allergic or severe adverse reactions to study medications; substance dependence <1 mo.; serious suicidal risk; required concurrent Tx with anticonvulsants, benzodiazepines (except for agitation/control of extrapyramidal signs), antidepressants, psychostimulants, AP drugs beyond those permitted; had contraindications for neuron imaging; had Hx of DSM–IV psychotic disorder with recovery; premorbid IQ of =70; ECT < 30 d	***G1:*** ***Age (mean±SD):*** 24.00±4.90 ***Males (n(%)):*** 111/132 (84.1%) ***Ethnicity:*** Caucasian 72/132 (54.6%) ***BL symptom scores:*** PANSS (mean±SD): 73.57±17.5 ***G2:*** ***Age (mean±SD):*** 23.50±4.60 ***Males (n(%)):*** 104/131 (79.4%) ***Ethnicity:*** Caucasian 67/131 (51.2%) ***BL symptom scores:*** PANSS (mean±SD): 75.9±18.07	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–20mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** once daily

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lindenmayer et al. 2007[110]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–IV–TR ***Study period:*** Sep 98 to May 2005 ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (Assignment after 1 wk of cross–titration from previous antipsychotic medication) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** Male and female, 18–60 yrs inpatients and outpatients at a state psychiatric hospital in New York who met DSM-IV-TR criteria for schizophrenia; Ps were required to have a PANSS total score of greater than 50, with a PANSS negative subscale score of greater than 20; negative symptom score was required to contain at least 3 out of 7 negative item scores of greater than 3; all pts fulfilled the criteria for the SDS. ***Main exclusion criteria:*** PANSS positive subscale score of greater than 20; SAS akathisia–item score of greater than 2; Hx of Tx failure on antipsychotics (persistent positive symptoms after 8 wks of treatment with adequate dosages of 1 or more antipsychotics); significant medical disorder; positive substance–abuse Dx in the last 3 months; PANSS depression item score (exclusion level greater than 4) was used to exclude patients with significant levels of depression as a secondary negative symptom; pregnant or breast feeding women and women of childbearing age not using adequate contraception	***G1:*** ***Age (mean±SD):*** 39.77±9.49 ***Males (n(%)):*** 19/19 (100%) ***Ethnicity:*** Caucasian 1/19 (5.3%) ***BL symptom scores:*** PANSS (mean±SD): 70.79±9.86 ***G2:*** ***Age (mean±SD):*** 39.02±10.48 ***Males (n(%)):*** 1/16 (6.3%) ***Ethnicity:*** Caucasian 67/131 (51.2%) ***BL symptom scores:*** PANSS (mean±SD): 71.25±17.46	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006[73]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan 2004 to Feb 2005 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Pts (≥18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder ***Main exclusion criteria:*** pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance–induced psychotic disorder	***G1:*** ***Age (mean±SD):*** 35.70±10.80 ***Males (n(%)):*** 42/57 (73.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42±11.3 ***G2:*** ***Age (mean±SD):*** 40.50±12.60 ***Males (n(%)):*** 27/53 (51%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.3±10.2 ***G3:*** ***Age (mean±SD):*** 39.00±11.00 ***Males (n(%)):*** 32/50 (64%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.6±10.4 ***G4:*** ***Age (mean±SD):*** 33.80±10.10 ***Males (n(%)):*** 37/52 (71.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.1±11 ***G5:*** ***Age (mean±SD):*** 38.60±12.90 ***Males (n(%)):*** 34/57 (59.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.3±9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–30mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 10–45mg ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–40 mg ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 50–1200 mg ***Intervals:*** NR ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–9 mg ***Intervals:*** NR ***G6:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–240 mg ***Intervals:*** NR

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: ***Age (mean±SD):*** 38.30±11.90 ***Males (n(%)):*** 26/50 (52%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.4±11	

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2000[124]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 19) ***Setting:*** Outpatient ***Country:*** Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (2–9d) ***Run-in phase performed:*** yes (1 month) ***Followup period:*** 54 wks	***Main inclusion criteria:*** Men and women aged 18–65 yrs who were within 5 yrs of their first exposure to neuroleptic treatment and had symptom severity at least in the mild range ***Main exclusion criteria:*** Pregnant or lactating, had prior medical histories of central nervous system disease or severe head injury, or if they had active serious illness or substance abuse disorders in the previous 30 d	***G1:*** ***Age (mean±SD):*** 28.83±6.52 ***Males (n(%)):*** 15/23 (65.2%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 33.17±7.88 ***G2:*** ***Age (mean±SD):*** 26.01±5.76 ***Males (n(%)):*** 17/21 (81%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 32.9±7.88 ***G3:*** ***Age (mean±SD):*** 31.77±11.24 ***Males (n(%)):*** 14/21 (66.7%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 30.29±6.73	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–6mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rosenheck et al. 2003[127]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** June 1998 to June 2000 ***Number of centers:*** Multicenter (n = 17) ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Industry (Eli Lilly, AstraZeneca) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Dx with SZ DSM–IV, schizoaffective disorder; outpatients with Hx of psychiatric hospitalization in previous 2 yrs; BPRS score≥ 36; serious symptoms and dysfunction for previous 2 yrs with inability to work or social constriction; ***Main exclusion criteria:*** Serious medical illness; unexplained seizures; severe medication allergies; had previously participated in olanzapine research.	***G1:*** ***Age (mean±SD):*** 46.20±7.70 ***Males (n(%)):*** 144/150 (96%) ***Ethnicity:*** Caucasian 59/150 (39.3%) ***BL symptom scores:*** BPRS (mean±SD): 48.7±8.5 PANSS (mean±SD): 85.2±15.5 ***G2:*** ***Age (mean±SD):*** 46.80±9.50 ***Males (n(%)):*** 154/159 (96.9%) ***Ethnicity:*** Caucasian 66/159 (41.5%) ***BL symptom scores:*** BPRS (mean±SD): 49.7±8.6 PANSS (mean±SD): 87.5±15.4	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Saddichha et al. 2008[129]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jun 2006 to Dec 2006 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** India ***Financial support:*** Declared no funding ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Dx of Sz DSM–IV; first episode; were completely drug–naïve ***Main exclusion criteria:*** Other psychiatric comorbidity; Hx of severe physical illness; alcohol, and substance abuse or dependence; Hx of preexisting diabetes or hypertension or family Hx of hypertension or diabetes mellitus	***G1:*** ***Age (mean±SD):*** 26.00±5.50 ***Males (n(%)):*** 16/31 (51.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 26.00±5.50 ***Males (n(%)):*** 18/35 (51.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 26.00±5.50 ***Males (n(%)):*** 18/33 (54.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 13.4+/-3.6mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 16.5+/-4.6mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4.4+/-1.2mg/d ***Intervals:*** NR
Sayers et al. 2005[130]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Government ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 26 wks	***Main inclusion criteria:*** DSM–IV diagnosis of schizophrenia and current cocaine abuse in the last 6 months; age 18–60; ability to provide informed consent ***Main exclusion criteria:*** use of depot medication within the past 6 months; Hx of sensitization to haloperidol or olanzapine or Hx of neuroleptic malignant syndrome; female pts who was pregnant, lactating, or not using contraceptives; unstable medical problems; homicidality or suicidality	***G1:*** ***Age (mean±SD):*** 45.90±6.20 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 45.90±6.20 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10 to 20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10 to 20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Sergi et al. 2007[134]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen and Forest, and Eli Lilly) ***Washout period performed:*** no(No washout period was used) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Sz patients DSM–IV age between 18–60 yrs old, competence to provide informed consent, no identifiable neurological conditions or mental retardation, and no alcohol or substance dependence in the last 6 months ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 50.00±5.80 ***Males (n(%)):*** 13/13 (100%) ***Ethnicity:*** Caucasian 4/13 (30.8%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 48.20±7.70 ***Males (n(%)):*** 24/28 (85.7%) ***Ethnicity:*** Caucasian 16/28 (57.1%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 49.20±6.70 ***Males (n(%)):*** 28/32 (87.5%) ***Ethnicity:*** Caucasian 9/32 (28.1%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 8mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smelson et al. 2006[136]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR Number of centers: Single center ***Setting:*** NR ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Met DSM–IV diagnostic criteria for cocaine dependence and Sz (made independently by a psychiatrist and a psychologist); showed any positive change in baseline craving following the presentation of cocaine cues ***Main exclusion criteria:*** met DSM–IV criteria for an additional Axis I disorder other than schizophrenia and cocaine dependence(subjects who abused, but were not dependent, on other substances were allowed in the study due to the high rate of polysubstance use among this population.); were taking other prescribed medications that could affect the central nervous system; Hx of seizures; were pregnant females; evidenced chronic disease of the central nervous system other than Sz	***G1:*** ***Age (mean±SD):*** 43.30±7.10 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 42.50±6.30 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** 5mg/d for the first 4 d, increased by 5mg/d every 4 d to a maximum dose of 20mg/d by d 12 and a target dose of 10mg/d. ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** 5mg/d for the first 4 d, increased by 5mg/d every 4 d to a maximum dose of 20mg/d by d 12 and a target dose of 10mg/d.

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smith et al. 2001[137]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Lilly) ***Washout period performed:*** yes (5–14d) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Medication refractory Pts with a Dx of Sz or schizoaffective psychosis, defined as a poor clinical response to at least two typical neuroleptics, with current active positive and/or severe negative symptoms which impacted on functioning and prevented discharge, patients had to be continuously hospitalized for at least 1 yr ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 43.00±6.70 ***Males (n(%)):*** 31/34 (91.2%) ***Ethnicity:*** Caucasian 9/34 (26.5%) ***BL symptom scores:*** PANSS (mean±SD): 80.4±8.2 ***G2:*** ***Age (mean±SD):*** 43.00±6.70 ***Males (n(%)):*** 31/34 (91.2%) ***Ethnicity:*** Caucasian 9/34 (26.5%) ***BL symptom scores:*** PANSS (mean±SD): 80.4±8.2	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–40mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tollefson et al. 1997[141]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 174) ***Setting:*** Mixed ***Country:*** International (North America and Europe) ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 14 mo	***Main inclusion criteria:*** Pts were required to have a minimum (BPRS) score of 18 (items extracted from the Positive and Negative Syndrome Scale and scored 0–6) and/or be intolerant of current antipsychotic therapy (excluding haloperidol) ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 38.30±11.10 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 34.1±11 MADRS (mean±SD): 16.7±8.7 PANSS (mean±SD): 92.1±20 ***G2:*** ***Age (mean±SD):*** 38.70±11.60 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** 33.1±10.6 MADRS (mean±SD): 16.6±8.9 PANSS (mean±SD): 90.1±19.2	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002[145]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** June 1996 to NR ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 14 wks	***Main inclusion criteria:*** Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs) defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS ***Main exclusion criteria:*** Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 90.4±11.6 ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 97.6±17.1 ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 91±13.5 ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 89.5±13.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** BID

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wright et al. 2001[147]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Inpatient ***Country:*** International (Australia, Austria, Belgium, Canada, Czech Republic, France, Greece, Hungary, Israel, South Africa, Spain, the United Kingdom, and United States) ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 24 h	***Main inclusion criteria:*** 18 yrs old or older, with a DSM–IV Dx of Sz, schizophreniform disorder, or schizoaffective disorder, an excited component score greater than or equal to 14 on the PANSS with a score of 4 or more on at least one item (1–7 point scale), clinically agitated and appropriate candidates for intramuscular treatment ***Main exclusion criteria:*** Pregnant or lactating women and patients with serious medical illnesses in which pharmacotherapy posed a substantial clinical risk or confounded Dx	***G1:*** ***Age (mean±SD):*** 38.20±11.60 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): NR ***G2:*** ***Age (mean±SD):*** 38.20±11.60 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 7.5 mg ***Intervals:*** 1–3 injections over a 24–hour period, optional second and third injections 2 or more and 4 or more hrs following the first injection ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10 mg ***Intervals:*** 1–3 injections over a 24–hour period, optional second and third injections 2 or more and 4 or more hrs following the first injection

Table 40. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wynn et al. 2007[148]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Unclear ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly, Janssen, F.P. Medications) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Age 18–60 yrs.; Dx with Sz, schizoaffective disorder (bipolar and depressive subtypes); competent to provide informed consent. ***Main exclusion criteria:*** Mental retardation, identifiable neurological conditions; alcohol and substance dependence in the last six months	***G1:*** ***Age (mean±SD):*** 50.30±6.20 ***Males (n(%)):*** 11/11 (100%) ***Ethnicity:*** Caucasian 4/11 (36.4%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 49.80±7.20 ***Males (n(%)):*** 17/21 (81%) ***Ethnicity:*** Caucasian 14/21 (66.7%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 46.80±8.30 ***Males (n(%)):*** 15/19 (79%) ***Ethnicity:*** Caucasian 6/19 (31.6%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 8mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECT = Electroconvulsive therapy; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms ; SAS = Simpson-Angus Scale ; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 41. Patient characteristics–haloperidol versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Arvanitis et al. 1997[46]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 26) ***Setting:*** Inpatient ***Country:*** USA, Canada, International ***Financial support:*** Industry (Zeneca) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts with Sz (18–65 yrs old) with acute exacerbation of chronic or subchronic Sz (DSM–III–R); BPRS score >26 with score of 3 on at least two items from BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), score of 4 on the CGI–S. ***Main exclusion criteria:*** Concurrent Axis I DSM–III–R diagnoses; Hx of seizure disorder; any clinically significant medical condition within 30 d; use of depot antipsychotics within one dosing interval; pregnancy	***G1:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** 42/52 (80.8%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 44±9 ***G2:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** 39/53 (73.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 45.7±10.9 ***G3:*** ***Age (mean±SD):*** 38.00±9.00 ***Males (n(%)):*** 39/48 (81.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 47.2±10.1 ***G4:*** ***Age (mean±SD):*** 38.00±9.00 ***Males (n(%)):*** 37/52 (71.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 45.3±10.9 ***G5:*** ***Age (mean±SD):*** 39.00±8.00 ***Males (n(%)):*** 38/51 (74.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 12mg/d ***Intervals:*** three equally divided doses ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 75mg/d ***Intervals:*** three equally divided doses ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 150mg/d ***Intervals:*** three equally divided doses ***G4:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 300mg/d ***Intervals:*** three equally divided doses ***G5:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 600mg/d ***Intervals:*** three equally divided doses ***G6:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 750mg/d ***Intervals:*** three equally divided doses

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			43.5±11.3 ***G6:*** ***Age (mean±SD):*** 35.00±10.00 ***Males (n(%)):*** 38/54 (70.4%) ***Ethnicity:*** Caucasian 54/69 (78.3%) ***BL symptom scores:*** BPRS (mean±SD): 45.7±11	
Atmaca et al. 2002[47]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Oct 2000 to Dec 2000 ***Number of centers:*** Single center ***Setting:*** Mixed ***Country:*** Turkey ***Financial support:*** NR ***Washout period performed:*** yes (2 wks) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Female Sz (DSM–IV) pts; 18–45 yrs old ***Main exclusion criteria:*** Severe physical illness; Hx of alcohol/substance abuse or dependence; presence of any endocrinological state, or taking oral contraceptives	***G1:*** ***Age (mean±SD):*** 29.44±10.08 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 49.67±4.23 PANSS (mean±SD): 90.54±7.34 ***G2:*** ***Age (mean±SD):*** 27.62±9.23 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.35±3.68 PANSS (mean±SD): 92.42±7.12	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 600mg/d ***Intervals:*** NR

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Copolov et al. 2000[68]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 55) ***Setting:*** Inpatient ***Country:*** 14 countries (Europe, Australia, South Africa) ***Financial support:*** Industry (AstraZeneca) ***Washout period performed:*** yes (48h) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Acute exacerbation of chronic or subchronic Sz; ≥18 yrs; CGI–S ≥ 4; PANSS ≥60; ≥4 on 2 or more PANSS items: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution. ***Main exclusion criteria:*** Significant co–morbidity, lab or ECG findings; epilepsy; WBC < the lower limit of the center's reference range; pregnant or lactating women, or not using adequate contraception; Tx with a long–acting depot medication < 1 dosing period prior to randomization; or participation in other investigational drug trial < 4 wks prior to randomization.	***G1:*** ***Age (mean±SD):*** 37.00±12.00 ***Males (n(%)):*** 147/227 (64.8%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** 158/221 (71.5%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–16mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 50–800mg/d ***Intervals:*** BID

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009[75]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 50) ***Setting:*** NR ***Country:*** 13 European countries and Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 mo	***Main inclusion criteria:*** recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 26.03±5.80 ***Males (n(%)):*** 32/52 (61.5%) ***Ethnicity:*** Caucasian 48/52 (92.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.35±19.4 ***G2:*** ***Age (mean±SD):*** 26.18±5.20 ***Males (n(%)):*** 40/60 (66.7%) ***Ethnicity:*** Caucasian 59/60 (98.3%) ***BL symptom scores:*** PANSS (mean±SD): 90.08±21.7 ***G3:*** ***Age (mean±SD):*** 26.07±5.60 ***Males (n(%)):*** 42/74 (56.8%) ***Ethnicity:*** Caucasian 70/74 (94.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.8±21.4 ***G4:*** ***Age (mean±SD):*** 25.56±5.90 ***Males (n(%)):*** 21/45 (46.7%) ***Ethnicity:*** Caucasian 43/45 (95.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.76±19.5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** NR

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Emsley et al. 2000[79]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** NR ***Country:*** South Africa, international ***Financial support:*** Industry (AstraZeneca) ***Washout period performed:*** NA ***Run-in phase performed:*** ***Drug:*** yes (4 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Pts (≥18 yrs) with Sz; Hx of partial response to conventional APs; persistent positive symptoms while previously taking AP; PANSS score ≥ 15 with ≥4 on one or more on following items: delusions, conceptual disorganization, hallucinatory behavior and suspiciousness/persecution; CGI–S score ≥ 3; partial or no response to 1 mo Tx with fluphenazine ***Main exclusion criteria:*** Known to be resistant to standard AP medication or clozapine; had acute exacerbation within past 3 mos.; known sensitivity to study drugs; Hx of idiopathic/drug–induced agranulocytosis	***G1:*** ***Age (mean±SD):*** 38.80±11.30 ***Males (n(%)):*** 101/145 (69.7%) ***Ethnicity:*** Caucasian 117/145 (80.7%) ***BL symptom scores:*** BPRS (mean±SD): 49.2±NR PANSS (mean±SD): 88.1±NR ***G2:*** ***Age (mean±SD):*** 37.70±10.80 ***Males (n(%)):*** 102/143 (71.3%) ***Ethnicity:*** Caucasian 113/143 (79%) ***BL symptom scores:*** BPRS (mean±SD): 49.4±NR PANSS (mean±SD): 88.2±NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 600mg/d ***Intervals:*** BID
Emsley et al. 2005[80]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Apr 2000 to Mar 2002 ***Number of centers:*** Multicenter ***Setting:*** Mixed ***Country:*** South Africa ***Financial support:*** Multiple sources (AstraZeneca) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** Apr 2000 to Mar 2002	***Main inclusion criteria:*** Pts (18–65 yrs) with clinically stable Sz or schizoaffective disorder (DSM–IV); on stable dose of AP; had TD ***Main exclusion criteria:*** another Axis I DSM–IV Dx; significant or unstable general medical condition; receiving clozapine	***G1:*** ***Age (mean±SD):*** 50.10±8.60 ***Males (n(%)):*** 15/23 (65.2%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 57±14.1 ***G2:*** ***Age (mean±SD):*** 49.20±14.50 ***Males (n(%)):*** 14/22 (63.6%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 55.5±12.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg ***Intervals:*** 2.5 mg increments ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 100–800mg ***Intervals:*** 100 mg increments

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Glick et al. 2005[65]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1998 to 2001 ***Number of centers:*** Multicenter (n = 3) ***Setting:*** NR ***Country:*** USA ***Financial support:*** Multiple sources (AstraZeneca) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 48 wks	***Main inclusion criteria:*** Pts requiring long–term therapy ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 44.00±12.80 ***Males (n(%)):*** 7/9 (77.8%) ***Ethnicity:*** Caucasian 4/9 (44.4%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 41.30±13.00 ***Males (n(%)):*** 13/16 (81.3%) ***Ethnicity:*** Caucasian 5/16 (31.3%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 200mg/wk ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 500mg/d ***Intervals:*** NR

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008[91]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Dec 2002 to Jan 2006 ***Number of centers:*** Multicenter (n = 50) ***Setting:*** Mixed ***Country:*** European countries, Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, Sanofi–Aventis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI ***Main exclusion criteria:*** More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts	***G1:*** ***Age (mean±SD):*** 25.40±5.60 ***Males (n(%)):*** 64/103 (90.3%) ***Ethnicity:*** Caucasian 93/103 (92.3%) ***BL symptom scores:*** PANSS (mean±SD): 88.9±19.8 ***G2:*** ***Age (mean±SD):*** 26.30±5.90 ***Males (n(%)):*** 67/105 (65.4%) ***Ethnicity:*** Caucasian 100/105 (95.2%) ***BL symptom scores:*** PANSS (mean±SD): 87.5±21.1 ***G3:*** ***Age (mean±SD):*** 26.40±5.70 ***Males (n(%)):*** 68/104 (50%) ***Ethnicity:*** Caucasian 97/104 (93.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.5±22.6 ***G4:*** ***Age (mean±SD):*** 26.70±5.70 ***Males (n(%)):*** 41/82 (46.7%) ***Ethnicity:*** Caucasian 77/82 (93.9%) ***BL symptom scores:*** PANSS (mean±SD): 88.3±20.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–16mg/d ***Intervals:*** NR

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006[73]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan 2004 to Feb 2005 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Pts (≥18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder ***Main exclusion criteria:*** Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance–induced psychotic disorder	***G1:*** ***Age (mean±SD):*** 35.70±10.80 ***Males (n(%)):*** 42/57 (73.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42±11.3 ***G2:*** ***Age (mean±SD):*** 40.50±12.60 ***Males (n(%)):*** 27/53 (51%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.3±10.2 ***G3:*** ***Age (mean±SD):*** 39.00±11.00 ***Males (n(%)):*** 32/50 (64%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.6±10.4 ***G4:*** ***Age (mean±SD):*** 33.80±10.10 ***Males (n(%)):*** 37/52 (71.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.1±11 ***G5:*** ***Age (mean±SD):*** 38.60±12.90 ***Males (n(%)):*** 34/57 (59.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.3±9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–30mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 10–45mg ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–40 mg ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 50–1200 mg ***Intervals:*** NR ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–9 mg ***Intervals:*** NR ***G6:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–240 mg ***Intervals:*** NR

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: ***Age (mean±SD):*** 38.30±11.90 ***Males (n(%)):*** 26/50 (52%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.4±11	

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2001[123]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** NR ***Country:*** Canada ***Financial support:*** Industry (Astra–Zeneca) ***Washout period performed:*** yes (48 h) ***Run-in phase performed:*** no ***Followup period:*** 6 mo	***Main inclusion criteria:*** Dx of Sz ***Main exclusion criteria:*** Hx of a serious medical disease or neurological disorder (including a history of serious head injury); active substance abuse in the 30–d period before enrollment.	***G1:*** ***Age (mean±SD):*** 25.40±5.60 ***Males (n(%)):*** 64/103 (90.3%) ***Ethnicity:*** Caucasian 93/103 (92.3%) ***BL symptom scores:*** PANSS (mean±SD): 88.9±19.8 ***G2:*** ***Age (mean±SD):*** 26.30±5.90 ***Males (n(%)):*** 67/105 (65.4%) ***Ethnicity:*** Caucasian 100/105 (95.2%) ***BL symptom scores:*** PANSS (mean±SD): 87.5±21.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 300–600mg/d ***Intervals:*** NR

Table 41. Patient characteristics–haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Velligan et al. 2002[143]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 34) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Industry (AstraZeneca) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 24 wks	***Main inclusion criteria:*** Conventional antipsychotic doses equivalent to 30mg/d or less of haloperidol; patients with full or partial remission; scores of 3 or less on BPRS; scores of moderately ill on the CGI–S ***Main exclusion criteria:*** Physical disorder or laboratory finding that made it inappropriate for them to receive study medication.	***G1:*** ***Age (mean±SD):*** 36.00±9.70 ***Males (n(%)):*** 13/15 (86.7%) ***Ethnicity:*** Caucasian 10/15 (66.7%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 39.12±10.76 ***Males (n(%)):*** 12/17 (70.6%) ***Ethnicity:*** Caucasian 9/17 (52.9%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 41.77±11.49 ***Males (n(%)):*** 18/26 (69.2%) ***Ethnicity:*** Caucasian 20/26 (76.9%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 12mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 300mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 600mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; WBC = White blood count; wk = week; yr = year

Table 42. Patient characteristics–haloperidol versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Apiquian et al. 2008[45]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Outpatient ***Country:*** Mexico ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Pts (17–50 yrs) Dx with Sz (DSM–IV), with acute psychosis; PANSS (positive) >16, score of at least 4 on at least two subscale items ***Main exclusion criteria:*** Other primary psychiatric or physical illnesses, current substance abuse or dependence, high risk for suicide or violence; or severe akathisia	***G1:*** ***Age (mean±SD):*** 28.50±7.20 ***Males (n(%)):*** 13/15 (86.7%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 77.8±10.5 ***G2:*** ***Age (mean±SD):*** 28.50±7.20 ***Males (n(%)):*** 12/17 (70.6%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 85.1±11.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2mg/d ***Intervals:*** nightly dosing ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1mg/d ***Intervals:*** nightly dosing
Blin et al. 1996[52]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** France ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Pts (18–50 yrs) with Sz (DSM–III–R) with acute exacerbation and symptoms of anxiety (Psychotic Anxiety Scale score at least 34) ***Main exclusion criteria:*** Schizo–affective disorders; severe somatic disorders; abnormal lab results; Hx of drug/alcohol abuse; pregnant/ lactating women; pts receiving long–acting antipsychotic agents during last 4 wks or short–acting antipsychotics during last 48 hrs or other treatments that might interfere with the trial medication or pt's emotional state	***G1:*** ***Age (mean±SD):*** 33.90±NR ***Males (n(%)):*** 11/20 (86.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 66.3±15.8 CGI-BP (mean±SD): 4.5±0.8 PANSS (mean±SD): 119±21.8 ***G2:*** ***Age (mean±SD):*** 34.80±NR ***Males (n(%)):*** 14/21 (66.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 70.1±12.2 CGI-BP (mean±SD): 4.6±0.8 PANSS (mean±SD): 124.4±19.7	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–12mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–12mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Borison et al. 1992[53]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** NR ***Country:*** USA ***Financial support:*** Industry (Janssen) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts with Sz (DSM–III–R); BPRS score at least 30, with 2 or more positive symptom items (unusual thought content, hallucinations, conceptual disorganization, suspiciousness); Baseline CGI of moderate or greater ***Main exclusion criteria:*** Clinically significant medical/neurological problems or concomitant psychiatric diagnoses, substance abuse or dependence	***G1:*** ***Age (mean±SD):*** 37.00±6.00 ***Males (n(%)):*** 12/12 (100%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 50±6 ***G2:*** ***Age (mean±SD):*** 43.00±9.00 ***Males (n(%)):*** 12/12 (100%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 52±5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–10mg/d ***Intervals:*** NR
Cavallaro et al. 2001[59]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Italy ***Financial support:*** Industry (Janssen) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (≤1 wk) ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts with subchronic Sz (DSM–II–R); able to consent; not treated with neuroleptics in past wk. or depot APs in past mo. ***Main exclusion criteria:*** Other major morbidity; substance/alcohol abuse; known hypersensitivity to included Tx; IQ <80.	***G1:*** ***Age (mean±SD):*** 23.20±2.30 ***Males (n(%)):*** 10/14 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 25.40±5.10 ***Males (n(%)):*** 12/15 (80%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.5–10mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2.5–10mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ceskova et al. 1993[60]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** ICD–9 ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Czech Republic ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts with Sz (ICD–9) ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 37.00±6.00 ***Males (n(%)):*** 12/12 (100%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 50±6 ***G2:*** ***Age (mean±SD):*** 43.00±9.00 ***Males (n(%)):*** 12/12 (100%) ***Ethnicity:*** Caucasian 6/12 (50%) ***BL symptom scores:*** BPRS (mean±SD): 52±5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–20mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Chouinard et al. 1993[61]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 6) ***Setting:*** Inpatient ***Country:*** Canada ***Financial support:*** Industry (Janssen) ***Washout period performed:*** yes (2 d to 2 wks) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts (18–65 yrs) with Dx of Sz; PANSS score 60–120; hospitalized for first 3 wks of the study; no depot neuroleptics for one treatment cycle ***Main exclusion criteria:*** Women: pregnant/lactating/without adequate contraception; mental disorder other than Sz; epilepsy; Hx of psychoactive substance/alcohol abuse; significant abnormal lab or ECG results	***G1:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 55.7±14.5 PANSS (mean±SD): 95.4±23.5 ***G2:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 53.6±14.9 PANSS (mean±SD): 93.9±22.7 ***G3:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 57.5±13.1 PANSS (mean±SD): 98±22.6 ***G4:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 50.8±12.7 PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 20mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 6mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 10mg/d ***Intervals:*** BID ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 16mg/d ***Intervals:*** BID

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			89.9±19.2 ***G5:*** ***Age (mean±SD):*** 37.00±10.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 54.5±12.6 PANSS (mean±SD): 94.3±21.3	

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001[62]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1996 to 2000 ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 14 wks	***Main inclusion criteria:*** Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs ***Main exclusion criteria:*** Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 31/37 (83.8%) ***Ethnicity:*** Caucasian 11/37 (29.7%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 34/40 (85%) ***Ethnicity:*** Caucasian 12/40 (30%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 33/39 (84.6%) ***Ethnicity:*** Caucasian 12/39 (30.8%) ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 35/41 (85.4%) ***Ethnicity:*** Caucasian 13/41 (31.7%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Claus et al. 1992[64]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 5) ***Setting:*** Inpatient ***Country:*** Belgium ***Financial support:*** Industry (Janssen) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** yes (2 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Pts (18–67 yrs) with chronic Sz (DSM–III–R); hospitalized <10 yrs ***Main exclusion criteria:*** Pts with clinically relevant organic diseases; pregnant/lactating women or in their reproductive phase without adequate contraceptive measures	***G1:*** ***Age (mean±SD):*** 39.00±NR ***Males (n(%)):*** 13/21 (61.9%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 79.8±21.12 ***G2:*** ***Age (mean±SD):*** 37.40±NR ***Males (n(%)):*** 15/21 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 91.1±18.79	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–10mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1–10mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Crespo-Facorro et al. 2006[71]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Feb–01 to Feb–05 ***Number of centers:*** Single center ***Setting:*** Mixed ***Country:*** Spain ***Financial support:*** Multiple sources (NR) ***Washout period performed:*** yes (3–5d) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (15–60 yrs) with Sz (DSM–IV); no AP within 6 wks; SAPS of moderate severity ***Main exclusion criteria:*** Mental retardation; drug dependence	***G1:*** ***Age (mean±SD):*** 28.30±8.70 ***Males (n(%)):*** 36/56 (64.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 62.4±10.9 YMRS (mean±SD): 9.3±4.3 ***G2:*** ***Age (mean±SD):*** 27.50±6.90 ***Males (n(%)):*** 33/55 (60%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 59.9±12.1 YMRS (mean±SD): 9.2±4.7 ***G3:*** ***Age (mean±SD):*** 26.10±7.60 ***Males (n(%)):*** 38/61 (62.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 56.8±10.3 YMRS (mean±SD): 8.8±4.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–9mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 3–6mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Csernansky et al. 2002[72]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** May–96 to Sep–98 ***Number of centers:*** Multicenter (n = 40) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Janssen) ***Washout period performed:*** yes (≤1 wks) ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Pts (18–65 yrs) with of Sz or schizoaffective disorder (DSM–IV) requiring hospitalization; clinically stable within last 30 d ***Main exclusion criteria:*** Another current DSM–IV Axis I Dx, an Axis II Dx of borderline personality disorder or antisocial personality disorder; substance dependence/abuse; clinically significant or unstable medical illness; current treatment with clozapine; Hx of refractoriness to AP; Tx with depot neuroleptic injections within one treatment cycle; allergic to either risperidone or haloperidol; pregnant/nursing women	***G1:*** ***Age (mean±SD):*** 40.10±10.40 ***Males (n(%)):*** 128/188 (68.1%) ***Ethnicity:*** Caucasian 93/188 (49.5%) ***BL symptom scores:*** PANSS (mean±SD): 67.3±17.4 ***G2:*** ***Age (mean±SD):*** 40.30±10.60 ***Males (n(%)):*** 127/77 (71.8%) ***Ethnicity:*** Caucasian 81/177 (45.8%) ***BL symptom scores:*** PANSS (mean±SD): 65±15.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** once/d ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–8mg/d ***Intervals:*** once/d
de Sena et al. 2003[77]	***Study design***: NonRCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** Mar–95 to Nov–97 ***Number of centers:*** Single center ***Setting:*** Unclear ***Country:*** Brazil ***Financial support:*** Industry (Janssen–Cilag) ***Washout period performed:*** yes (3–7d) ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Pts (15–40 yrs) with Sz (DSM–III–R) ***Main exclusion criteria:*** Long hospitalization (≥12 months); other Axis I disorders; drug dependence; significant neurological or organic disorders; Pts difficult to follow–up; participation in a trial during 4 wks prior to the study; use of depot neuroleptics with one treatment cycle before the start of the study	***G1:*** ***Age (mean±SD):*** 27.40±NR ***Males (n(%)):*** 13/13 (100%) ***Ethnicity:*** Caucasian 2/13 (15.4%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 27.90±NR ***Males (n(%)):*** 20/20 (100%) ***Ethnicity:*** Caucasian 4/20 (20%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–17mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1–6mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Emsley et al. 1999[81]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 61) ***Setting:*** Inpatient ***Country:*** Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, Sweden ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (15–45 yrs) with Sz or schizophreniform disorder (DSM–III–R) without prior Tx; had psychotic symptoms requiring Tx; had received a maximum of 3 d of ED Tx for this disorder; had no clinically relevant neurological, ECG or lab test abnormalities; informed consent ***Main exclusion criteria:*** Pregnant/lactating women or of reproductive age not using adequate contraception; other mental illness; psychoactive substance abuse; previous depot antipsychotic Tx; clinically significant organic disease; participated in clinical trials of investigational drugs within 4 wks	***G1:*** ***Age (mean±SD):*** 24.00±NR ***Males (n(%)):*** 54/84 (64.3%) ***Ethnicity:*** Caucasian 62/84 (73.8%) ***BL symptom scores:*** BPRS (mean±SD): 89.6±20.16 CGI-S (mean±SD): 51.5±8.62 ***G2:*** ***Age (mean±SD):*** 26.00±NR ***Males (n(%)):*** 68/99 (68.7%) ***Ethnicity:*** Caucasian 62/99 (62.6%) ***BL symptom scores:*** BPRS (mean±SD): 89.1±18.81 CGI-S (mean±SD): 51.1±10.89	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–10mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–10mg/d ***Intervals:*** BID
Fakra et al. 2008[82]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–IV–TR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** France ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 50 wks	***Main inclusion criteria:*** Pts (18–55 yrs) with Sz (DSM–IV) ***Main exclusion criteria:*** Hx of alcohol/drug abuse; comorbidity with depressive or anxiety disorders; chronic medical illness other than Sz; facial TD; taking depot antipsychotics	***G1:*** ***Age (mean±SD):*** 37.80±11.40 ***Males (n(%)):*** 12/14 (85.7%) ***Ethnicity:*** Caucasian 13/14 (92.9%) ***BL symptom scores:*** PANSS (mean±SD): 75.21±8.65 ***G2:*** ***Age (mean±SD):*** 33.90±9.50 ***Males (n(%)):*** 7/11 (63.6%) ***Ethnicity:*** Caucasian 10/11 (90.9%) ***BL symptom scores:*** PANSS (mean±SD): 76.1±15.46	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** NR ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Heck et al. 2000[85]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** 1993 to 1995 ***Number of centers:*** Multicenter (n = 12) ***Setting:*** Mixed ***Country:*** Netherlands ***Financial support:*** Industry (Janssen–Cilag) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** NR	***Main inclusion criteria:*** Pts (18–70 yrs) with Sz (DSM–III–R); clinically stable on current meds; score of at least 5 on ESRS or use anti-Parkinson medication ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 44.50±NR ***Males (n(%)):*** 12/22 (54.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 40.00±NR ***Males (n(%)):*** 13/25 (52%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–24mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–16mg/d ***Intervals:*** BID
Kee et al. 1998[99]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** yes (<1 wks) ***Run-in phase performed:*** yes (3 wks) ***Followup period:*** NR	***Main inclusion criteria:*** Sz disorder based on the Structured Clinical Interview for DSM–III–R, treatment–resistant ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 37.67±8.37 ***Males (n(%)):*** 7/9 (77.8%) ***Ethnicity:*** Caucasian 5/9 (55.6%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 35.00±9.72 ***Males (n(%)):*** 5/9 (55.6%) ***Ethnicity:*** Caucasian 5/9 (55.6%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 6mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2003[100]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** NR ***Country:*** USA ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** yes (<1 wks) ***Run-in phase performed:*** no ***Followup period:*** NR	***Main inclusion criteria:*** Dx with Sz by DSM–IV criteria were assessed; Pts were included in the study only if their age ranged between 18–55 ***Main exclusion criteria:*** If English was not their first language, not having any of the target symptoms (autonoetic agnosia: thought insertion, voices arguing, voices commenting, made feelings, made acts, or made impulses)	***G1:*** ***Age (mean±SD):*** 33.90±11.70 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 36.6±6 ***G2:*** ***Age (mean±SD):*** 33.90±11.70 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 36.6±6 ***G3:*** ***Age (mean±SD):*** NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.5–10.0mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 2.5–10.0mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2.0–8.0mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2006[101]	***Study design:*** RCT ***Registration #:*** F1D–MC–HGGN ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** July 1999–Nov 2000 to July 1999–Nov 2001 ***Number of centers:*** Multicenter (n = 39) ***Setting:*** Mixed ***Country:*** USA, Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 52 wks	***Main inclusion criteria:*** 18–55yrs; schizophrenia or schizoaffective disorder; PANSS score ≥ 4 on at least 2 positive items; BPRS score ≥18; English speaking; have a level of understanding sufficient to agree to all tests and examinations; had illness duration of at least 2 yrs from first hospitalization and/or diagnosis/treatment; female pts of childbearing potential must have been using a medically accepted means of contraception. ***Main exclusion criteria:*** Previous participation in present study, participated in a clinical trial of another investigational drug within 1 mo.; participated in a study within the past 3 mo. that included the neurocognitive battery; significant neurological disorder, head injury with loss of consciousness; serious illness such that death was anticipated within 1 yr or intensive care hospitalization was anticipated within 6 mo, QTc interval greater than 450 ms, uncorrected hypo– or hyperthyroidism, current agranulocytosis, female patients who were either pregnant or nursing, allergic reaction to study medication, DSM–IV substance dependence) within past 2 mo, Tx with depot antipsychotics, reversible MAO inhibitor within 2 wks, or clozapine or ECT within 1 mo.	***G1:*** ***Age (mean±SD):*** 39.80±8.32 ***Males (n(%)):*** 69/97 (71.1%) ***Ethnicity:*** Caucasian 51/97 (52.6%) ***BL symptom scores:*** MADRS (mean±SD): 14.4±10.2 PANSS (mean±SD): 82.7±14.1 ***G2:*** ***Age (mean±SD):*** 38.40±7.90 ***Males (n(%)):*** 115/159 (72.3%) ***Ethnicity:*** Caucasian 95/159 (59.8%) ***BL symptom scores:*** MADRS (mean±SD): 13.2±8.7 PANSS (mean±SD): 82.6±13.1 ***G3:*** ***Age (mean±SD):*** 39.50±8.25 ***Males (n(%)):*** 111/158 (70.3%) ***Ethnicity:*** Caucasian 101/158 (63.9%) ***BL symptom scores:*** MADRS (mean±SD): 14.1±9.3 PANSS (mean±SD): 84.1±14.7	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–19mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–10mg/d

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010[102]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** *Two–center* ***Setting:*** Outpatient ***Country:*** South Korea ***Financial support:*** Other (Choi Shine Hae 2008–2009) ***Washout period performed:*** yes (>4wks) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Pts with Sz, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all participants were smokers; they were clinically stable, with no changes in their antipsychotic medication prescriptions. ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 42.50±8.70 ***Males (n(%)):*** 25/35 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 37.10±4.80 ***Males (n(%)):*** 23/31 (74.2%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 41.80±11.40 ***Males (n(%)):*** 23/32 (71.9%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G4:*** ***Age (mean±SD):*** 39.90±12.80 ***Males (n(%)):*** 28/41 (68.3%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15.9+/-7.1mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 21.7+/-5.5 mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15.9+/-4.3mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4.8+/-2.9mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lee et al. 2007[107]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Two–center* ***Setting:*** Inpatient ***Country:*** Taiwan ***Financial support:*** Government ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Sz Pt identified on the basis of ICD–9 ***Main exclusion criteria***: no previous Hx of other functional psychosis, neurological illnesses/insults, substance abuse within the past 2 yrs; Hx of substance dependence, electroconvulsive therapy within the past 6 months, or any other significant current medical conditions	***G1:*** ***Age (mean±SD):*** 27.20±10.40 ***Males (n(%)):*** 10/10 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 89.5±15.2 ***G2:*** ***Age (mean±SD):*** 25.90±7.25 ***Males (n(%)):*** 10/10 (100%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 94.2±9.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 7.6+/-2.6mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4.1+/-0.8mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lim et al. 2010[151]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar disorder and Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Dec 2005 to Sept 2006 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** South Korea ***Financial support:*** Industry (Janssen) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 24 h	***Main inclusion criteria:*** Age 18–65 yrs; manifestation of acute psychotic agitation in the ED or inpatient ward; Sz or schizoaffective disorder, bipolar I disorder with or without psychotic features, delusional disorders, or psychotic disorder not otherwise specified; symptom score of ≥ 14 on the 5–item acute agitation cluster derived from the PANSS–EC; score of ≥ 3 on the CGI–S ***Main exclusion criteria:*** Neurological disorders or severe medical diseases; alcohol or other psychoactive substance abusers; treated with any antipsychotics or benzodiazepines within 6 h of enrollment; Hx of neuroleptic malignant syndrome or hypersensitivity to trial medications; treated with a depot antipsychotic within 1 Tx cycle of enrollment; eligible women were tested for pregnancy; pregnant and lactating women	***G1:*** ***Age (mean±SD):*** 34.70±10.20 ***Males (n(%)):*** 32/62 (51.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 32.30±9.80 ***Males (n(%)):*** 34/62 (54.8%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–15mg ***Intervals:*** could repeat every 2 hr (max 15mg/24 hr) ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–6mg ***Intervals:*** could repeat every 2 hr (max 6mg/24 hr)

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Liu et al. 2000[111]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** Taiwan ***Financial support:*** NR ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 12 wk	***Main inclusion criteria:*** Prominent clinical symptoms as revealed by a total score of > 65 on the PANSS ***Main exclusion criteria:*** Patients with a previous history of physical illness or substance abuse that cast the Dx in doubt	***G1:*** ***Age (mean±SD):*** 35.10±13.00 ***Males (n(%)):*** 6/19 (31.6%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 86.1±14.9 ***G2:*** ***Age (mean±SD):*** 32.70±8.40 ***Males (n(%)):*** 9/19 (47.4%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 76±16.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** NR ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Marder et al. 1994[114]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 20) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Janssen–Ortho) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Dx of Sz otherwise physically healthy; PANSS total score ≥60, ≤120 ***Main exclusion criteria:*** Schizoaffective disorder; women with childbearing potential	***G1:*** ***Age (mean±SD):*** 38.00±10.00 ***Males (n(%)):*** 60/66 (90.9%) ***Ethnicity:*** Caucasian 41/66 (62.1%) ***BL symptom scores:*** BPRS (mean±SD): 54.6±10.7 PANSS (mean±SD): 92.9±17.4 ***G2:*** ***Age (mean±SD):*** 39.30±10.90 ***Males (n(%)):*** 54/63 (85.7%) ***Ethnicity:*** Caucasian 41/63 (65.1%) ***BL symptom scores:*** BPRS (mean±SD): 51.5±10.2 PANSS (mean±SD): 87.4±17.6 ***G3:*** ***Age (mean±SD):*** 10.00±11.10 ***Males (n(%)):*** 55/64 (85.9%) ***Ethnicity:*** Caucasian 42/64 (65.6%) ***BL symptom scores:*** BPRS (mean±SD): 54.1±11.7 PANSS (mean±SD): 93.8±19.1 ***G4:*** ***Age (mean±SD):*** 36.20±9.80 ***Males (n(%)):*** 61/65 (93.9%) ***Ethnicity:*** Caucasian 42/65 (64.6%)	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 20mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2mg/d ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 6mg/d ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 10mg/d ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 16mg/d

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			BL symptom scores: BPRS (mean±SD): 54±11.8 PANSS (mean±SD): 92.5±19.4 ***G5:*** ***Age (mean±SD):*** 36.50±10.40 ***Males (n(%)):*** 53/64 (82.8%) ***Ethnicity:*** Caucasian 38/64 (59.4%) ***BL symptom scores:*** BPRS (mean±SD): 54.2±10.5 PANSS (mean±SD): 93.8±17.2	

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Marder et al. 2003[113]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV Study period: NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen Research ***Foundation)*** ***Washout period performed:*** NA ***Run-in phase performed:*** yes (2 wks) ***Followup period:*** 2 yrs	***Main inclusion criteria:*** All subjects were 18–60 yrs of age; had at least two documented episodes of acute schizophrenic illness or at least 2 yrs of continuing psychotic symptoms; had been outpatients for at least 1 month; and were considered candidates for maintenance therapy with an antipsychotic ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 43.30±8.40 ***Males (n(%)):*** 29/30 (96.7%) ***Ethnicity:*** Caucasian 14/30 (46.7%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 43.70±9.20 ***Males (n(%)):*** 29/33 (87.9%) ***Ethnicity:*** Caucasian 14/33 (42.4%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2mg TID. for the first week and then 6mg h.s. ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2mg TID. for the first week and then 6mg h.s.

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006[73]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan 2004 to Feb 2005 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Pts (≥18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder ***Main exclusion criteria:*** Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance–induced psychotic disorder	***G1:*** ***Age (mean±SD):*** 35.70±10.80 ***Males (n(%)):*** 42/57 (73.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42±11.3 ***G2:*** ***Age (mean±SD):*** 40.50±12.60 ***Males (n(%)):*** 27/53 (51%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.3±10.2 ***G3:*** ***Age (mean±SD):*** 39.00±11.00 ***Males (n(%)):*** 32/50 (64%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.6±10.4 ***G4:*** ***Age (mean±SD):*** 33.80±10.10 ***Males (n(%)):*** 37/52 (71.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.1±11 ***G5:*** ***Age (mean±SD):*** 38.60±12.90 ***Males (n(%)):*** 34/57 (59.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.3±9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–30mg ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 10–45mg ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–40 mg ***G4:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 50–1200 mg ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–9 mg ***G6:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–240 mg

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: ***Age (mean±SD):*** 38.30±11.90 ***Males (n(%)):*** 26/50 (52%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.4±11	

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Min et al. 1993[117]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Mixed ***Country:*** Korea ***Financial support:*** NR ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Chronic Sz; age 18–65 yrs.; PANSS score >60 and <120; normal laboratory and ECG tests; hospitalized d 6–14 if possible ***Main exclusion criteria:*** Other mental disorder; clinically significant co–morbidity; epilepsy; Hx of alcohol–or drug abuse within 12–month; included in other investigational drug trial within 4 wks; women not on adequate contraception, pregnant or lactating	***G1:*** ***Age (mean±SD):*** 34.10±NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.8±14.8 PANSS (mean±SD): 88.2±28.2 ***G2:*** ***Age (mean±SD):*** 34.10±NR ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 53.4±18.4 PANSS (mean±SD): 92±30	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2.5–5mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2.5–5mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Moller et al. 2008[118]	***Study design:*** RCT ***Registration #:*** NCTOOI59081 ***Study population:*** Schizophrenia ***DSM Classification:*** ICD–10 F20 ***Study period***: Nov 2000 to May 2004 ***Number of centers:*** Multicenter (n = 13) ***Setting:*** Inpatient ***Country:*** Germany ***Financial support:*** Multiple sources (Janssen–Cilag) ***Washout period performed:*** yes (1 wk) ***Run-in phase performed:*** no ***Followup period:*** 2 yrs	***Main inclusion criteria:*** Having recovered from a first illness episode with a diagnosis according to ICD–10 F20, whereas first episode was pragmatically defined as the first inpatient treatment of psychotic symptoms; age between 18–55 yrs; having either participated in the acute Tx study or being suited for lateral entry; being sufficiently able in German language; having given consent after extensive information about the various phases and ramifications of the 2–yr study ***Main exclusion criteria:*** Pregnancy; insufficient response to pretreatment with risperidone or haloperidol; other contraindications for risperidone or haloperidol; mental retardation; organic brain disease; substance abuse; Hx of suicidal behavior; severe physical disease; participation in other trials	***G1:*** ***Age (mean±SD):*** 30.70±10.00 ***Males (n(%)):*** 80/146 (54.8%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 80.8±24.8 YMRS (mean±SD): 5.5±5.5 ***G2:*** ***Age (mean±SD):*** 29.50±9.50 ***Males (n(%)):*** 92/143 (64.3%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 77.3±23 YMRS (mean±SD): 5±5.2	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–8mg/d ***Intervals:*** Once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–8mg/d ***Intervals:*** Once daily

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Peuskens et al. 1995[120]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 110) ***Setting:*** Inpatient ***Country:*** International (15 countries) ***Financial support:*** NR ***Washout period performed:*** yes (3–7d) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Dx of chronic Sz disorder according to DSM–III–R with a total score between 60–120 on the PANSS ***Main exclusion criteria:*** Clinically significant organic or neurological disorders, epilepsy, psychiatric disorders other than chronic schizophrenia, a history of alcohol or drug abuse in the previous 12 months, or had participated in trials of investigational drugs in the preceding 4 wks; pregnant or lactating women and those of reproductive age without adequate contraception	***G1:*** ***Age (mean±SD):*** 38.10±NR ***Males (n(%)):*** 150/226 (66.4%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.1±10.22 PANSS (mean±SD): 90.1±17.86 ***G2:*** ***Age (mean±SD):*** 38.40±NR ***Males (n(%)):*** 166/229 (72.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.9±10.59 PANSS (mean±SD): 32.9±7.88 ***G3:*** ***Age (mean±SD):*** 38.10±NR ***Males (n(%)):*** 152/227 (67%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.6±10.09 PANSS (mean±SD): 89.6±17.48 ***G4:*** ***Age (mean±SD):*** 37.60±NR ***Males (n(%)):*** 144/230 (62.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 48.1±10.92 PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10mg/d ***Intervals:*** 2 times per d distributed evenly ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1mg/d ***Intervals:*** 2 times per d distributed evenly ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4mg/d ***Intervals:*** 2 times per d distributed evenly ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 8mg/d ***Intervals:*** 2 times per d distributed evenly ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 12mg/d ***Intervals:*** 2 times per d distributed evenly ***G6:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 16mg/d ***Intervals:*** 2 times per d distributed evenly

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			89.2±18.81 ***G5:*** ***Age (mean±SD):*** 37.90±NR ***Males (n(%)):*** 142/226 (62.8%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 49.1±10.07 PANSS (mean±SD): 90.5±18.04 ***G6:*** ***Age (mean±SD):*** 38.50± ***Males (n(%)):*** 140/224 (62.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 49.5±10.63 PANSS (mean±SD): 89.8±17.96	

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2000[124]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 19) ***Setting:*** Outpatient ***Country:*** Canada ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (2–9d) ***Run-in phase performed:*** yes (1 month) ***Followup period:*** 54 wks	***Main inclusion criteria:*** Men and women aged 18–65 yrs who were within 5 yrs of their first exposure to neuroleptic treatment and had symptom severity at least in the mild range ***Main exclusion criteria:*** Pregnant or lactating, had prior medical histories of central nervous system disease or severe head injury, or if they had active serious illness or substance abuse disorders in the previous 30 d	***G1:*** ***Age (mean±SD):*** 28.83±6.52 ***Males (n(%)):*** 15/23 (65.2%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 33.17±7.88 ***G2:*** ***Age (mean±SD):*** 26.01±5.76 ***Males (n(%)):*** 17/21 (81%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 32.9±7.88 ***G3:*** ***Age (mean±SD):*** 31.77±11.24 ***Males (n(%)):*** 14/21 (66.7%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 30.29±6.73	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–6mg/d
Remillard et al. 2008[125]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Outpatient ***Country:*** Canada, France ***Financial support:*** Industry (Janssen–Ortho) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Dx of Sz with DSM–III–R ***Main exclusion criteria:*** no Hx of drug or alcohol abuse or neurological disease	***G1:*** ***Age (mean±SD):*** 44.10±9.40 ***Males (n(%)):*** 11/14 (78.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 40.60±9.90 ***Males (n(%)):*** 11/14 (78.6%) ***Ethnicity:*** NR ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–40mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–6mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Schooler et al. 2005[132]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period***: Nov 1996 to Jan 2000 ***Number of centers:*** Multicenter (n = 12) ***Setting:*** Outpatient ***Country:*** Australia, Austria, Canada, Finland, France, Germany, Israel, Netherlands, New Zealand, South Africa, UK, USA ***Financial support:*** Industry (Johnson and Johnson) ***Washout period performed:*** yes (3–7d) ***Run-in phase performed:*** no ***Followup period:*** 2 yrs	***Main inclusion criteria:*** Age 16–45yrs; Sz, schizophreniform disorder, or schizoaffective disorder ≤ 1 yr; no more than two psychiatric hospitalizations for psychosis; <12 wks of cumulative exposure to APs; required AP Tx upon enrollment ***Main exclusion criteria:*** Meeting DSM–IV criteria for another axis I diagnosis, including substance dependence or abuse; needing another nonantipsychotic psychotropic medication at enrollment; having a serious or unstable medical illness	***G1:*** ***Age (mean±SD):*** 25.70±6.87 ***Males (n(%)):*** 200/277 (72.2%) ***Ethnicity:*** Caucasian 208/277 (75.1%) ***BL symptom scores:*** PANSS (mean±SD): 81.1±20.1 ***G2:*** ***Age (mean±SD):*** 25.20±6.84 ***Males (n(%)):*** 196/278 (70.5%) ***Ethnicity:*** Caucasian 205/277 (73.7%) ***BL symptom scores:*** PANSS (mean±SD): 83.7±20.22	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–8mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1–8mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Sergi et al. 2007[134]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen and Forest, and Eli Lilly) ***Washout period performed:*** no(No washout period was used) ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Sz patients DSM–IV age between 18–60 yrs old, competence to provide informed consent, no identifiable neurological conditions or mental retardation, and no alcohol or substance dependence in the last 6 months ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 50.00±5.80 ***Males (n(%)):*** 13/13 (100%) ***Ethnicity:*** Caucasian 4/13 (30.8%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 48.20±7.70 ***Males (n(%)):*** 24/28 (85.7%) ***Ethnicity:*** Caucasian 16/28 (57.1%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 49.20±6.70 ***Males (n(%)):*** 28/32 (87.5%) ***Ethnicity:*** Caucasian 9/32 (28.1%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 8mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4mg/d ***Intervals:*** NR
Shrivastava et al. 2000[135]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** India ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** yes (2–4 wks) ***Followup period:*** 12 mo	***Main inclusion criteria:*** Admitted for acute exacerbation of Sz ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 31.80±4.80 ***Males (n(%)):*** 30/50 (60%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 89.1±4.8 ***G2:*** ***Age (mean±SD):*** 36.20±3.50 ***Males (n(%)):*** 29/50 (58%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 91.9±5.9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tamrakar et al. 2006[139]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** ICD–10 ***Study period:*** Jan 2002 to Jun 2002 ***Number of centers:*** *Single center* ***Setting:*** NR ***Country:*** Nepal ***Financial support:*** NR ***Washout period performed:*** yes (1 wk for oral; 4 wks for depot) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts between 18–45 yrs of age Dx with Sz according to ICD–10 ***Main exclusion criteria:*** Pts with comorbid psychiatric and medical illnesses	***G1:*** ***Age (mean±SD):*** 28.67±4.16 ***Males (n(%)):*** 10/18 (55.6%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 88.56±13.35 ***G2:*** ***Age (mean±SD):*** 27.28±4.38 ***Males (n(%)):*** 12/18 (66.7%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 88.17±15.7	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–6mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002[145]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** June 1996 to NR ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen, Eli Lilly, Novartis, Merck) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 14 wks	***Main inclusion criteria:***Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of Tx presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs, defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS ***Main exclusion criteria:*** Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization	***G1:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 90.4±11.6 ***G2:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 97.6±17.1 ***G3:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 91±13.5 ***G4:*** ***Age (mean±SD):*** 40.80±9.20 ***Males (n(%)):*** 133/167 (79.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 89.5±13.8	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–30mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 10–40mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4–16mg/d ***Intervals:*** BID

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wirshing et al. 1999[146]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** *Two–center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Multiple sources (Janssen) ***Washout period performed:*** yes (3–7d) ***Run-in phase performed:*** yes (3 wks) ***Followup period:*** 8 wks	***Main inclusion criteria:*** Age 18–60 yrs: Dx of Sz; considered Tx resistant; able to take oral medication; BPRS ≥ 45; minimum score of 4 on two BPRS items: conceptual disorganization, suspiciousness, hallucinations, or unusual thought content; CGI ≥ 4. Meet treatment refractory requirement. ***Main exclusion criteria:*** Had experienced a period of good functioning within 5 yrs; clinically significant neurologic disease; seizure disorder; Hx of head injury; physical, cognitive, or language impairment that would affect ratings; substance abuse within 6 mo.; previous trial of risperidone sufficient to determine clinical response; Tx with investigational drugs or clozapine within 4 wks; depot neuroleptics within 8 wks; behavior that posed significant danger to self or others; significant clinical improvement between the initial screening and the start of the study.	***G1:*** ***Age (mean±SD):*** 40.00±8.20 ***Males (n(%)):*** 29/33 (87.9%) ***Ethnicity:*** Caucasian 16/33 (48.5%) ***BL symptom scores:*** BPRS (mean±SD): 70.8±14.6 ***G2:*** ***Age (mean±SD):*** 41.00±9.40 ***Males (n(%)):*** 26/34 (76.5%) ***Ethnicity:*** Caucasian 20/34 (58.8%) ***BL symptom scores:*** BPRS (mean±SD): 66.8±14.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 6mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wynn et al. 2007[148]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 3) ***Setting:*** Unclear ***Country:*** USA ***Financial support:*** Multiple sources (Eli Lilly, Janssen, F.P. Medications) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 8 wks	***Main inclusion criteria:*** Age 18–60 yrs.; Dx with Sz, schizoaffective disorder (bipolar and depressive subtypes); competent to provide informed consent. ***Main exclusion criteria:*** Mental retardation, identifiable neurological conditions; alcohol and substance dependence in the last six months	***G1:*** ***Age (mean±SD):*** 50.30±6.20 ***Males (n(%)):*** 11/11 (100%) ***Ethnicity:*** Caucasian 4/11 (36.4%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 49.80±7.20 ***Males (n(%)):*** 17/21 (81%) ***Ethnicity:*** Caucasian 14/21 (66.7%) ***BL symptom scores:*** NR ***G3:*** ***Age (mean±SD):*** 46.80±8.30 ***Males (n(%)):*** 15/19 (79%) ***Ethnicity:*** Caucasian 6/19 (31.6%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 8mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 15mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 4mg/d ***Intervals:*** NR

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Yen et al. 2004[149]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** NR ***Country:*** Taiwan ***Financial support:*** Government ***Washout period performed:*** yes (7 d from oral neuroleptics; 4 wks for depot preparations) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** Age 18–65 yrs.; Dx with Sz; total PANSS score >60 ***Main exclusion criteria:*** Suffering from psychoses other than Sz, with early childhood brain damage, unable to comply with the medication, with a severe illness (including hematological, hepatic, or cardiovascular disease; pulmonary embolism; alcoholism or addiction), and pregnant or lactating women.	***G1:*** ***Age (mean±SD):*** 34.00±6.61 ***Males (n(%)):*** 11/20 (55%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 90.2±16.4 ***G2:*** ***Age (mean±SD):*** 32.90±10.30 ***Males (n(%)):*** 15/21 (71.4%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 90.5±16.5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–20mg/d ***Intervals:*** Once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–12mg/d ***Intervals:*** Once daily
Zhang et al. 2001[150]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** China ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** yes (2 wks) ***Followup period:*** 12 wks	***Main inclusion criteria:*** Inpatients in Beijing Huilongguan Hospital; DSM–III–R criteria for schizophrenia; Pts Tx with three conventional neuroleptics for at least 3 months at full dose; duration of illness for at least 5 yrs; age between 25–60 yrs, with a CGI scale ratings of a score of 4 or higher ***Main exclusion criteria:*** Significant medical illness or were actively abusing alcohol or illegal drugs	***G1:*** ***Age (mean±SD):*** 43.70±8.10 ***Males (n(%)):*** 30/37 (81.1%) ***Ethnicity:*** Caucasian 0/37 (0%) ***BL symptom scores:*** PANSS (mean±SD): 79.3±21.7 ***G2:*** ***Age (mean±SD):*** 43.80±6.40 ***Males (n(%)):*** 30/41 (73.2%) ***Ethnicity:*** Caucasian 0/41 (0%) ***BL symptom scores:*** PANSS (mean±SD): 82.4±22.4	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 6mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 20mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; ; ED = Emergency Department; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; QTc = Corrected QT interval; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 43. Patient characteristics–haloperidol versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Brook et al. 2005[57]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** 1996 to NR ***Number of centers:*** Multicenter ***Setting:*** Inpatient ***Country:*** International ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** Pts (18–70 yrs) with acute exacerbation of Sz or schizoaffective disorder (DSM–IV); BPRS score of 40 or more ***Main exclusion criteria:*** Previous Tx with other psychoactive drugs including antidepressants/mood stabilizers and/or significant past medical Hx; previous substance abuse or organic mental disease; Immediate risk of harm to oneself or others	***G1:*** ***Age (mean±SD):*** 34.60±10.50 ***Males (n(%)):*** 91/138 (65.9%) ***Ethnicity:*** Caucasian 110/138 (79.7%) ***BL symptom scores:*** BPRS (mean±SD): 57±9.6 ***G2:*** ***Age (mean±SD):*** 34.00±10.50 ***Males (n(%)):*** 286/429 (66.7%) ***Ethnicity:*** Caucasian 338/429 (78.8%) ***BL symptom scores:*** BPRS (mean±SD): 57±10.5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** IM: 2.5–10mg/d; Oral: 5–20mg/d ***Intervals:*** IM: every 2 h (if needed); Oral: BID ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** IM: 10–40mg/d; Oral: 40–80mg/d ***Intervals:*** IM: every 2 h (if needed); Oral: BID
Corripio et al. 2005[69]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** Spain ***Financial support:*** Multiple sources (Pfizer) ***Washout period performed:*** yes (2 wks) ***Run-in phase performed:*** no ***Followup period:*** 2 wks	***Main inclusion criteria:*** Pts with Sz (DSM–IV) manifesting acute psychotic exacerbation ***Main exclusion criteria:*** Hx of substance abuse; past or present neurological disease; other organic disturbance; pregnancy	***G1:*** ***Age (mean±SD):*** 36.00±9.00 ***Males (n(%)):*** 4/10 (40%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 79.6±16.5 ***G2:*** ***Age (mean±SD):*** 30.70±5.00 ***Males (n(%)):*** 6/10 (60%) ***Ethnicity:*** NR ***BL symptom scores:*** PANSS (mean±SD): 74.7±9.7	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** ≤4 inj (5mg) every 2hr for 2–3 d ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 10–40mg/d ***Intervals:*** ≤4 inj (5mg) every 2hr for 2–3 d

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009[75]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 50) ***Setting:*** NR ***Country:*** 13 European countries and Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 6 mo	***Main inclusion criteria:*** recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 26.03±5.80 ***Males (n(%)):*** 32/52 (61.5%) ***Ethnicity:*** Caucasian 48/52 (92.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.35±19.4 ***G2:*** ***Age (mean±SD):*** 26.18±5.20 ***Males (n(%)):*** 40/60 (66.7%) ***Ethnicity:*** Caucasian 59/60 (98.3%) ***BL symptom scores:*** PANSS (mean±SD): 90.08±21.7 ***G3:*** ***Age (mean±SD):*** 26.07±5.60 ***Males (n(%)):*** 42/74 (56.8%) ***Ethnicity:*** Caucasian 70/74 (94.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.8±21.4 ***G4:*** ***Age (mean±SD):*** 25.56±5.90 ***Males (n(%)):*** 21/45 (46.7%) ***Ethnicity:*** Caucasian 43/45 (95.6%) ***BL symptom scores:*** PANSS (mean±SD): 86.76±19.5	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** NR

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Goff et al. 1998[83]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 6) ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** yes (≥1 wks) ***Run-in phase performed:*** no ***Followup period:*** 4 wks	***Main inclusion criteria:*** Hospitalized ≤2 wks for acute exacerbation; hospitalized or resided in an intermediate treatment center ≥ 3 mo; had partially responded to neuroleptic Tx; BPRS total score ≥ 25; score ≥ 4 on one or more of the core items of the Psychosis subscale (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content); ***Main exclusion criteria:*** Women of child–bearing potential; comorbid Axis I psychiatric disorders; significant medical or neurologic disorders; had received a depot neuroleptic within 2 months or had recently used an illicit drug.	***G1:*** ***Age (mean±SD):*** 35.50±7.50 ***Males (n(%)):*** 16/17 (94.1%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 35.4±NR ***G2:*** ***Age (mean±SD):*** 41.70±9.00 ***Males (n(%)):*** 17/19 (89.5%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 34.2±NR ***G3:*** ***Age (mean±SD):*** 39.20±10.00 ***Males (n(%)):*** 16/17 (94.1%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 33.4±NR ***G4:*** ***Age (mean±SD):*** 38.10±7.90 ***Males (n(%)):*** 16/17 (94.1%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 31.5±NR ***G5:*** ***Age (mean±SD):*** 41.70±9.00 ***Males (n(%)):*** 19/20 (95%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 36.3±NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 15mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 4mg/d ***Intervals:*** BID ***G3:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 10mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40mg/d ***Intervals:*** BID ***G5:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 160mg/d ***Intervals:*** BID

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hirsch et al. 2002[86]	***Study design***: NonRCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** NR ***Number of centers:*** Multicenter (n = 52) ***Setting:*** Outpatient ***Country:*** Europe ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** yes (2 wks) ***Run-in phase performed:*** yes (≤2 wks) ***Followup period:*** 28 wks	***Main inclusion criteria:*** Pts (18–64 yrs) with chronic/subchronic Sz; required AP maintenance Tx; PANSS–negative score = >10; GAF score >30; women unable to conceive or were reliably using contraception and were not pregnant or lactating ***Main exclusion criteria:*** Having an acute exacerbation; hospitalized for psychosis in previous 12 wks; score of ≥ 5 on PANSS item P7 or G8; deteriorated between baseline and screening (CGI–I score > 6); Hx of substance abuse or dependence in past 3 mo.; at significant risk of suicide or homicide; Hx of allergy to any neuroleptic; neuroleptic malignant syndrome; failure to experience therapeutic response to APs at least twice in the previous 2 yrs; had taken part in a ziprasidone trial or had received an investigational drug within 4 wks, fluoxetine within 5 wks, monoamine oxidase inhibitors within 2 wks, or antidepressants or lithium within 1 week; relevant medical illness, epilepsy, neurologic disorders, HIV seropositivity, serological evidence of hepatitis infection, or clinically significant ECG or lab abnormalities	***G1:*** ***Age (mean±SD):*** 39.40±NR ***Males (n(%)):*** NR ***Ethnicity:*** Caucasian 93/103 (90.3%) ***BL symptom scores:*** BPRS (mean±SD): 9.7±3.6 MADRS (mean±SD): 14.1±7.9 PANSS (mean±SD): 74.4±16.1 ***G2:*** ***Age (mean±SD):*** 39.20±NR ***Males (n(%)):*** NR ***Ethnicity:*** Caucasian 100/105(95.2%) ***BL symptom scores:*** BPRS (mean±SD): 9.6±3.7 MADRS (mean±SD): 15±8.3 PANSS (mean±SD): 72.9±17.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–15mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 80–160mg/d ***Intervals:*** BID

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008[91]	***Study design:*** RCT ***Registration #:*** ISRCTN68736636 ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Dec 2002 to Jan 2006 ***Number of centers:*** Multicenter (n = 50) ***Setting:*** Mixed ***Country:*** European countries, Israel ***Financial support:*** Industry (AstraZeneca, Pfizer, Sanofi–Aventis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI ***Main exclusion criteria:*** More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts	***G1:*** ***Age (mean±SD):*** 25.40±5.60 ***Males (n(%)):*** 64/103 (62.1%) ***Ethnicity:*** Caucasian 93/103 (90.3%) ***BL symptom scores:*** PANSS (mean±SD): 88.9±19.8 ***G2:*** ***Age (mean±SD):*** 26.30±5.90 ***Males (n(%)):*** 67/105 (63.8%) ***Ethnicity:*** Caucasian 100/105(95.2%) ***BL symptom scores:*** PANSS (mean±SD): 87.5±21.1 ***G3:*** ***Age (mean±SD):*** 26.40±5.70 ***Males (n(%)):*** 68/104 (65.4%) ***Ethnicity:*** Caucasian 97/104 (93.3%) ***BL symptom scores:*** PANSS (mean±SD): 91.5±22.6 ***G4:*** ***Age (mean±SD):*** 26.70±5.70 ***Males (n(%)):*** 41/82 (50%) ***Ethnicity:*** Caucasian 77/82 (93.9%) ***BL symptom scores:*** PANSS (mean±SD): 88.3±20.1	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 1–4mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–750mg/d ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–16mg/d ***Intervals:*** NR

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006[73]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan 2004 to Feb 2005 ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Pts (≥18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder ***Main exclusion criteria:*** Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance–induced psychotic disorder	***G1:*** ***Age (mean±SD):*** 35.70±10.80 ***Males (n(%)):*** 42/57 (73.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42±11.3 ***G2:*** ***Age (mean±SD):*** 40.50±12.60 ***Males (n(%)):*** 27/53 (51%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.3±10.2 ***G3:*** ***Age (mean±SD):*** 39.00±11.00 ***Males (n(%)):*** 32/50 (64%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.6±10.4 ***G4:*** ***Age (mean±SD):*** 33.80±10.10 ***Males (n(%)):*** 37/52 (71.2%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.1±11 ***G5:*** ***Age (mean±SD):*** 38.60±12.90 ***Males (n(%)):*** 34/57 (59.7%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.3±9	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 4–30mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 10–45mg ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–40 mg ***Intervals:*** NR ***G4:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 50–1200 mg ***Intervals:*** NR ***G5:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–9 mg ***Intervals:*** NR ***G6:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–240 mg ***Intervals:*** NR

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: ***Age (mean±SD):*** 38.30±11.90 ***Males (n(%)):*** 26/50 (52%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 43.4±11	

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Miceli et al. 2010[116]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** *Single center* ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** yes (10 d) ***Run-in phase performed:*** no ***Followup period:*** 2–3 d	***Main inclusion criteria:*** The study included adults (aged =18 yrs) with a Hx of Sz or schizoaffective disorder in whom long–term antipsychotic therapy was indicated; Pts were also required to have had normal findings on screening and baseline clinical laboratory testing ***Main exclusion criteria:*** Ps were excluded if they had a Hx of acute exacerbation of psychosis within 3 months before the study; had clinically significant abnormal findings on ECG or a condition with a potential to affect ECG findings; had received electroconvulsive therapy within 6 months before the study; had used fluphenazine decanoate or haloperidol decanoate within 4 months before the study; had used fluoxetine within 5 wks before the study; had used clozapine or investigational drugs within 4 wks before the study; or had used other anTIDepressants or lithium, mood stabilizers, or anticonvulsants within 2 wks before the study	***G1:*** ***Age (mean±SD):*** 43.60±NR ***Males (n(%)):*** 21/27 (77.8%) ***Ethnicity:*** Caucasian 12/27 (44.4%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 43.70±NR ***Males (n(%)):*** 25/31 (80.7%) ***Ethnicity:*** Caucasian 13/31 (41.9%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 7.5–10 mg ***Intervals:*** every 4 hrs ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 20–30 mg ***Intervals:*** every 4 hrs

Table 43. Patient characteristics–haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Potkin et al. 2009[122]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM–III–R ***Study period:*** July 1994 to Sep 2000 ***Number of centers:*** Multicenter (n = 40) ***Setting:*** NR ***Country:*** USA, Canada ***Financial support:*** Industry (Pfizer) ***Washout period performed:*** yes (4 wk) ***Run-in phase performed:*** no ***Followup period:*** 3.75 yrs	***Main inclusion criteria:*** A chronic or subchronic Sz or schizoaffective disorder (DSM–III–R) Dx, no hospitalization for psychosis for at least 12 wk prior to screening, PANSS negative score >10, PANSS hostility and uncooperativeness item scores <4 (moderate), CGI–I score<6 (much worse) at baseline (compared to screening), GAF Scale score >30 ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 40.00±NR ***Males (n(%)):*** NR ***Ethnicity:*** Caucasian 110/151 (72.9%) ***BL symptom scores:*** PANSS (mean±SD): 72.6±18.1 ***G2:*** ***Age (mean±SD):*** 39.30±NR ***Males (n(%)):*** NR ***Ethnicity:*** Caucasian 146/221 (66.1%) ***BL symptom scores:*** PANSS (mean±SD): 72.5±17.7 ***G3:*** ***Age (mean±SD):*** 39.90±NR ***Males (n(%)):*** NR ***Ethnicity:*** Caucasian 165/227 (72.7%) ***BL symptom scores:*** PANSS (mean±SD): 73.7±18.3	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–20mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 80–120mg/d ***Intervals:*** NR ***G3:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 80–160mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; ; ED = Emergency Department; FGA = first-generation antipsychotic; GAF = Global Assessment of Functioning; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; QTc = Corrected QT interval; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; WBC = White blood count; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 44. Patient characteristics–perphenazine versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2007[93]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Aug 2000 to Mar 2001 ***Number of centers:*** Multicenter (n = 59) ***Setting:*** Outpatient ***Country:*** USA, Canada ***Financial support:*** Industry (Bristol–Myers Squibb) ***Washout period performed:*** yes (2–14d) ***Run-in phase performed:*** yes (4–6 wks) ***Followup period:*** 6 wks	***Main inclusion criteria:*** > 18 yrs. Sz; Tx resistant with Olanzapine, Risperidone; PANSS≥75. CGI–S≥4; At least 2 of: conceptual disorganization, suspiciousness, hallucinatory behavior, delusions. Tx as outpatient for one 3 month period in last 2 yrs. ***Main exclusion criteria:*** Dx of schizoaffective disorder; residual Sz; bipolar disorder; presentation or Hx consistent with delirium; dementia; amnesia or other cognitive disorders; refractory response to prior clozapine or perphenazine; likely to require prohibited concomitant therapy; current or recent psychoactive drug or alcohol abuse or dependence; Hx of suicidal attempts or thoughts; known allergy to study drugs; Tx with an investigational drug within 4 wk of washout phase; previous enrollment in an aripiprazole clinical study; had other acute or unstable medical condition; pregnant or lactating	***G1:*** ***Age (mean±SD):*** 41.60±10.87 ***Males (n(%)):*** 94/146 (64.4%) ***Ethnicity:*** Caucasian 75/146 (51.4%) ***BL symptom scores:*** BPRS (mean±SD): 17.6±3.34 PANSS (mean±SD): 99.5±15.61 ***G2:*** ***Age (mean±SD):*** 42.60±12.40 ***Males (n(%)):*** 114/154 (74%) ***Ethnicity:*** Caucasian 76/154 (49.4%) ***BL symptom scores:*** BPRS (mean±SD): 17.2±2.86 PANSS (mean±SD): 97.5±15.62	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** 8–64mg/d ***Intervals:*** BID if > 8mg/d ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15–30mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 45. Patient characteristics–perphenazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ascher-Svanum et al. 2008[131]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** May–98 to Sep–02 ***Number of centers:*** Multicenter (n = 21) ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Multiple sources (NR) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** aged >18 years; DSM–IV criteria for Sz, schizoaffective or schizophreniform disorders based on the SCID; minimum score of 18 on BPRS ***Main exclusion criteria:*** serious or unstable physical illnesses; high risk of suicide; lactating or pregnant women and individuals with medical conditions contraindicating use of any study medication	***G1:*** ***Age (mean±SD):*** 44.20±11.90 ***Males (n(%)):*** 28/48 (58.3%) ***Ethnicity:*** Caucasian 27/48(52.3%) ***BL symptom scores:*** BPRS (mean±SD): 28.9±31.90 PANSS (mean±SD): 81.0±18.9 ***G2:*** ***Age (mean±SD):*** 42.70±12.20 ***Males (n(%)):*** 138/222 (62.1%) ***Ethnicity:*** Caucasian 124/222 (55.9%) ***BL symptom scores:*** BPRS (mean±SD): 31.9±11.30 PANSS (mean±SD): 87.10±19.60	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** NR ***Intervals:*** NR

Table 45. Patient characteristics–perphenazine versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005[23]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan–01 to Dec–04 ***Number of centers:*** Multicenter (n = 57) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 18 mo	***Main inclusion criteria:*** Age 18–65 yrs; Dx of Sz; able to take oral AP medication ***Main exclusion criteria:*** Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one Sz episode; Hx of Tx resistance; pregnant or breast feeding; other serious and unstable medical condition	***G1:*** ***Age (mean±SD):*** 40.00±11.10 ***Males (n(%)):*** 199/261 (76.3%) ***Ethnicity:*** Caucasian 152/261 (58.2%) ***BL symptom scores:*** PANSS (mean±SD): 74.3±18.1 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** Caucasian 196/336 (58.3%) ***BL symptom scores:*** PANSS (mean±SD): 76.1±18.2 ***G3:*** ***Age (mean±SD):*** 40.90±11.20 ***Males (n(%)):*** 255/337 (75.7%) ***Ethnicity:*** Caucasian 213/337 (63.2%) ***BL symptom scores:*** PANSS (mean±SD): 75.7±16.9 ***G4:*** ***Age (mean±SD):*** 40.60±11.30 ***Males (n(%)):*** 253/341 (74.2%) ***Ethnicity:*** Caucasian 204/301 (59.8%) ***BL symptom scores:*** PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** 8–32mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5–30mg/d ***Intervals:*** once daily ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1.5–6.0mg/d ***Intervals:*** once daily ***G5:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** BID

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 ***G5:*** ***Age (mean±SD):*** 40.10±11.00 ***Males (n(%)):*** 129/185 (69.7%) ***Ethnicity:*** Caucasian 109/185 (58.9%) ***BL symptom scores:*** PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 46. Patient characteristics–perphenazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005[23]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan–01 to Dec–04 ***Number of centers:*** Multicenter (n = 57) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 18 mo	***Main inclusion criteria:*** Age 18–65 yrs; Dx of Sz; able to take oral AP medication ***Main exclusion criteria:*** Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition	***G1:*** ***Age (mean±SD):*** 40.00±11.10 ***Males (n(%)):*** 199/261 (76.3%) ***Ethnicity:*** Caucasian 152/261 (58.2%) ***BL symptom scores:*** PANSS (mean±SD): 74.3±18.1 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** Caucasian 196/336 (58.3%) ***BL symptom scores:*** PANSS (mean±SD): 76.1±18.2 ***G3:*** ***Age (mean±SD):*** 40.90±11.20 ***Males (n(%)):*** 255/337 (75.7%) ***Ethnicity:*** Caucasian 213/337 (63.2%) ***BL symptom scores:*** PANSS (mean±SD): 75.7±16.9 ***G4:*** ***Age (mean±SD):*** 40.60±11.30 ***Males (n(%)):*** 253/341 (74.2%) ***Ethnicity:*** Caucasian 204/301 (59.8%) ***BL symptom scores:*** PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** 8–32mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5–30mg/d ***Intervals:*** once daily ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1.5–6.0mg/d ***Intervals:*** once daily ***G5:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** BID

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 ***G5:*** ***Age (mean±SD):*** 40.10±11.00 ***Males (n(%)):*** 129/185 (69.7%) ***Ethnicity:*** Caucasian 109/185 (58.9%) ***BL symptom scores:*** PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 47. Patient characteristics–perphenazine versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ascher-Svanum et al. 2008[131]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** May–98 to Sep–02 ***Number of centers:*** Multicenter (n = 21) ***Setting:*** Mixed ***Country:*** USA ***Financial support:*** Multiple sources (NR) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 12 mo	***Main inclusion criteria:*** aged >18 years; DSM–IV criteria for Sz, schizoaffective or schizophreniform disorders based on the SCID; minimum score of 18 on BPRS ***Main exclusion criteria:*** serious or unstable physical illnesses; high risk of suicide; lactating or pregnant women and individuals with medical conditions contraindicating use of any study medication	***G1:*** ***Age (mean±SD):*** 44.20±11.90 ***Males (n(%)):*** 28/48 (58.3%) ***Ethnicity:*** Caucasian 27/48(52.3%) ***BL symptom scores:*** BPRS (mean±SD): 28.9±31.90 PANSS (mean±SD): 81.0±18.9 ***G2:*** ***Age (mean±SD):*** 42.00±11.80 ***Males (n(%)):*** 130/217 (60.0%) ***Ethnicity:*** Caucasian 118/217 (54.3%) ***BL symptom scores:*** BPRS (mean±SD): 32.4±12.20 PANSS (mean±SD): 87.40±20.70	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** NR ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** NR ***Intervals:*** NR

Table 47. Patient characteristics–perphenazine versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005[23]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan–01 to Dec–04 ***Number of centers:*** Multicenter (n = 57) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 18 mo	***Main inclusion criteria:*** Age 18–65 yrs; Dx of Sz; able to take oral AP medication ***Main exclusion criteria:*** Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition.	***G1:*** ***Age (mean±SD):*** 40.00±11.10 ***Males (n(%)):*** 199/261 (76.3%) ***Ethnicity:*** Caucasian 152/261 (58.2%) ***BL symptom scores:*** PANSS (mean±SD): 74.3±18.1 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** Caucasian 196/336 (58.3%) ***BL symptom scores:*** PANSS (mean±SD): 76.1±18.2 ***G3:*** ***Age (mean±SD):*** 40.90±11.20 ***Males (n(%)):*** 255/337 (75.7%) ***Ethnicity:*** Caucasian 213/337 (63.2%) ***BL symptom scores:*** PANSS (mean±SD): 75.7±16.9 ***G4:*** ***Age (mean±SD):*** 40.60±11.30 ***Males (n(%)):*** 253/341 (74.2%) ***Ethnicity:*** Caucasian 204/301 (59.8%) ***BL symptom scores:*** PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** 8–32mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5–30mg/d ***Intervals:*** once daily ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1.5–6.0mg/d ***Intervals:*** once daily ***G5:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** BID

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 ***G5:*** ***Age (mean±SD):*** 40.10±11.00 ***Males (n(%)):*** 129/185 (69.7%) ***Ethnicity:*** Caucasian 109/185 (58.9%) ***BL symptom scores:*** PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 48. Patient characteristics–perphenazine versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005[23]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** DSM IV ***Study period:*** Jan–01 to Dec–04 ***Number of centers:*** Multicenter (n = 57) ***Setting:*** Outpatient ***Country:*** USA ***Financial support:*** Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis) ***Washout period performed:*** NA ***Run-in phase performed:*** no ***Followup period:*** 18 mo	***Main inclusion criteria:*** Age 18–65 yrs; Dx of Sz; able to take oral AP medication ***Main exclusion criteria:*** Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition.	***G1:*** ***Age (mean±SD):*** 40.00±11.10 ***Males (n(%)):*** 199/261 (76.3%) ***Ethnicity:*** Caucasian 152/261 (58.2%) ***BL symptom scores:*** PANSS (mean±SD): 74.3±18.1 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** Caucasian 196/336 (58.3%) ***BL symptom scores:*** PANSS (mean±SD): 76.1±18.2 ***G3:*** ***Age (mean±SD):*** 40.90±11.20 ***Males (n(%)):*** 255/337 (75.7%) ***Ethnicity:*** Caucasian 213/337 (63.2%) ***BL symptom scores:*** PANSS (mean±SD): 75.7±16.9 ***G4:*** ***Age (mean±SD):*** 40.60±11.30 ***Males (n(%)):*** 253/341 (74.2%) ***Ethnicity:*** Caucasian 204/301 (59.8%) ***BL symptom scores:*** PANSS (mean±SD):	***G1:*** ***Classification:*** FGA ***Drug:*** Perphenazine ***Dosage:*** 8–32mg/d ***Intervals:*** once daily ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 7.5–30mg/d ***Intervals:*** once daily ***G3:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 200–800mg/d ***Intervals:*** BID ***G4:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1.5–6.0mg/d ***Intervals:*** once daily ***G5:*** ***Classification:*** SGA ***Drug:*** Ziprasidone ***Dosage:*** 40–160mg/d ***Intervals:*** BID

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 ***G5:*** ***Age (mean±SD):*** 40.10±11.00 ***Males (n(%)):*** 129/185 (69.7%) ***Ethnicity:*** Caucasian 109/185 (58.9%) ***BL symptom scores:*** PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 49. Patient characteristics–trifluoperazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rinieris et al. 1980[157]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Schizophrenia ***DSM Classification:*** NR ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Greece ***Financial support:*** NR ***Washout period performed:*** NA ***Run-in phase performed:*** yes (1 wk) ***Followup period:*** 6 wks	***Main inclusion criteria:*** Sz pts with absence of clinical symptoms; no Hx of thyroid or endocrinological disease; no use of psychotropic meds ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.5±9.3 ***G2:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 40.5±10 ***G3:*** ***Age (mean±SD):*** 27.30±9.00 ***Males (n(%)):*** NR ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 36.4±11.4	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 50–100mg ***Intervals:*** TID ***G2:*** ***Classification:*** FGA ***Drug:*** Trifluoperazine ***Dosage:*** 2.5–5mg ***Intervals:*** TID ***G3:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 50–100mg ***Intervals:*** TID

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; wk = week; yr = year

B) Bipolar Disorder

Table 50. Patient characteristics–chlorpromazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Barbini et al. 1997[48]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** Italy ***Financial support:*** NR ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** Bipolar inpatients with a manic episode, according to DSM IV criteria ***Main exclusion criteria:*** Other axis I diagnoses, history of alcohol or substance abuse, medication with long–acting neuroleptics during a period of 6 months before the study	***G1:*** ***Age (mean±SD):*** 40.90±8.90 ***Males (n(%)):*** 2/12 (16.7%) ***Ethnicity:*** NR ***BL symptom scores:*** YMRS (mean±SD): 34.10±8.00 ***G2:*** ***Age (mean±SD):*** 33.20±10.90 ***Males (n(%)):*** 8/15 (53.3%) ***Ethnicity:*** NR ***BL symptom scores:*** YMRS (mean±SD): 38.30±4.20	***G1:*** ***Classification:*** FGA ***Drug:*** Chlorpromazine ***Dosage:*** 2mg/kg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Clozapine ***Dosage:*** 25mg/d ***Intervals:*** NR

AP = antipsychotic; BL = baseline; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 51. Patient characteristics–haloperidol versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Vieta et al. 2005[32]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM IV ***Study period:*** Dec 2003 to Jun 2004 ***Number of centers:*** Multicenter (n = 76) ***Setting:*** Inpatient ***Country:*** Spain ***Financial support:*** Industry (Bristol–Myers Squibb, Otsuka) ***Washout period performed:*** yes (1–3 days) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** DSM–IV Dx of bipolar I disorder. ***Main exclusion criteria:*** Presence of rapid–cycling bipolar I disorder; duration of the current manic episode of more than 4 weeks; proven substance misuse; Pts considered unresponsive to antipsychotics.	***G1:*** ***Age (mean±SD):*** 41.00 ± 11.80 ***Males (n(%)):*** 57/172 (31.9%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 4.90 ± 1.31 YMRS (mean±SD): 31.50 ± 7.87 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 5.00 ± 1.32 YMRS (mean±SD): 31.10 ±6.61	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–15mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15–30mg ***Intervals:*** NR

Table 51. Patient characteristics–haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Young et al. 2009[33]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 59) ***Setting:*** Inpatient ***Country:*** Bulgaria, Croatia, Mexico, Peru, Russia, South Africa, USA ***Financial support:*** Industry (Bristol–Myers Squibb, Otsuka) ***Washout period performed:*** yes (2–4 wks) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** with bipolar I disorder manic or mixed type (with or without psychotic features), who were experiencing an acute relapse requiring hospitalization ***Main exclusion criteria:*** Sz or schizoaffective disorder, or if they were experiencing their first manic or mixed episode; previously unresponsive to Tx for manic symptoms	***G1:*** ***Age (mean±SD):*** 41.60 ± NR ***Males (n(%)):*** 72/165 (43.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 454.10 ± 10.15 CGI (mean±SD): 4.40 ± 1.27 YMRS (mean±SD): 27.60 ± 5.67 ***G2:*** ***Age (mean±SD):*** 40.50 ± NR ***Males (n(%)):*** 72/167 (43.1%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 554.80 ± 10.31 CGI (mean±SD): 4.50 ± 1.29 YMRS (mean±SD): 28.01 ±5.77	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–10mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15–30mg/d ***Intervals:*** NR

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 52. Patient characteristics–haloperidol versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Moreno et al. 2007[119]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** outpatient ***Country:*** Brazil ***Financial support:*** Foundation (NR) ***Washout period performed:*** yes (4 days) ***Run-in phase performed:*** no ***Followup period:*** 6 wk	***Main inclusion criteria:*** Bipolar pts had not switched from a depression phase to mania or from mania phase to depression, within 1 month ***Main exclusion criteria:*** A serious general medical condition or neurological disease, evidence of primary sleep disorder or a previous history of drug or alcohol abuse	***G1:*** ***Age (mean±SD):*** 39.20 ± 11.20 ***Males (n(%)):*** 59/185 (31.9%) ***Ethnicity:*** Caucasian 61/185 (33%) ***BL symptom scores:*** CGI-BP (mean±SD): 13.00 ± 2.00 YMRS (mean±SD): 30.60 ± 8.60 ***G2:*** ***Age (mean±SD):*** 38.60 ± 14.20 ***Males (n(%)):*** 63/175 (42.8%) ***Ethnicity:*** Caucasian 70/175 (40%) ***BL symptom scores:*** CGI-BP (mean±SD): 11.30 ± 1.80 YMRS (mean±SD): 30.60 ± 5.00	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

Table 52. Patient characteristics–haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tohen et al. 2003[140]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 58) ***Setting:*** Mixed ***Country:*** International (North America and Europe) ***Financial support:*** Industry (Eli Lilly) ***Washout period performed:*** yes (7 days) ***Run-in phase performed:*** no ***Followup period:*** 12 wk	***Main inclusion criteria:*** DSM–IV criteria for bipolar disorder manic or mixed type (with or without psychotic features) ***Main exclusion criteria:*** DSM–IV substance dependence	***G1:*** ***Age (mean±SD):*** 40.00 ± 13.00 ***Males (n(%)):*** 94/219 (42.9%) ***Ethnicity:*** NR ***BL symptom scores:*** CGI-BP (mean±SD): 30.60 ± 7.68 ***G2:*** ***Age (mean±SD):*** 41.00 ± 13.00 ***Males (n(%)):*** 86/234 (36.8%) ***Ethnicity:*** NR ***BL symptom scores:*** CGI-BP (mean±SD): 31.10 ± 7.57	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–15mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Olanzapine ***Dosage:*** 5–20mg/d ***Intervals:*** NR

AP = antipsychotic; BL = baseline; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 53. Patient characteristics–haloperidol versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McIntyre et al. 2005[115]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** Jan–01 to Apr–02 ***Number of centers:*** Multicenter (n = 4) ***Setting:*** Inpatient ***Country:*** International ***Financial support:*** Industry (AstraZeneca) ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** DSM–IV diagnosis of bipolar I disorder, current episode manic, with or without psychotic features. ***Main exclusion criteria:*** Received treatment with clozapine within 28 days of the start of the trial, had an index manic episode judged to be the direct physiological consequence of a medical condition, treatment, or substance abuse	***G1:*** ***Age (mean±SD):*** 45.10 ± NR ***Males (n(%)):*** 36/98 (36.7%) ***Ethnicity:*** NR ***BL symptom scores:*** YMRS (mean±SD): 32.30 ± NR ***G2:*** ***Age (mean±SD):*** 42.80 ± NR ***Males (n(%)):*** 37/101 (36.6%) ***Ethnicity:*** NR ***BL symptom scores:*** YMRS (mean±SD): 34.00 ± NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–8mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Quetiapine ***Dosage:*** 100–800mg/d ***Intervals:*** BID

AP = antipsychotic; BID = Twice daily; BL = baseline; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 54. Patient characteristics–haloperidol versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Janicak et al. 2001[90]	***Study design***: RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Multicenter (n=3) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Janssen) ***Washout period performed:*** yes (4–6d) ***Run-in phase performed:*** no ***Followup period:*** 6 wks	***Main inclusion criteria:*** bipolar subtype/manic phase, had not received depot antipsychotics or fluoxetine in the 4 weeks before ***Main exclusion criteria:*** A Dx of alcohol or substance abuse within 6 months of admission, hypersensitivity to haloperidol or risperidone	***G1:*** ***Age (mean±SD):*** 41.80 ± NR ***Males (n(%)):*** 59/185 (31.9%) ***Ethnicity:*** Caucasian 61/185 (33%) ***BL symptom scores:*** NR ***G2:*** ***Age (mean±SD):*** 41.90 ± NR ***Males (n(%)):*** 63/175 (36%) ***Ethnicity:*** Caucasian 70/175 (40%) ***BL symptom scores:*** NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 5–17mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1–6mg/d ***Intervals:*** BID
Sachs et al. 2002[128]	***Study design***: RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Multicenter (NR) ***Setting:*** Inpatient ***Country:*** USA ***Financial support:*** Industry (Janssen) ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 3 wks	***Main inclusion criteria:*** bipolar disorder and at least 1 prior manic episode ***Main exclusion criteria:*** alcohol or substance abuse	***G1:*** ***Age (mean±SD):*** 42.70 ± 12.38 ***Males (n(%)):*** 30/53 (56.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 41.20 ± 10.92 YMRS (mean±SD): 27.30 ± 5.82 ***G2:*** ***Age (mean±SD):*** 41.40 ± 10.82 ***Males (n(%)):*** 26/52 (50.0%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 42.50 ± 10.82 YMRS (mean±SD): 28.00 ± 5.77	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 3–12mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 2–6mg/d ***Intervals:*** BID

Table 54. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Segal et al. 1998[133]	***Study design***: RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Single center ***Setting:*** Inpatient ***Country:*** South Africa ***Financial support:*** Industry (Janssen) ***Washout period performed:*** no ***Run-in phase performed:*** no ***Followup period:*** 28 days	***Main inclusion criteria:*** bipolar with acute manic episode ***Main exclusion criteria:*** NR	***G1:*** ***Age (mean±SD):*** 29.50 ± NR ***Males (n(%)):*** 5/15 (33.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 15.20 ± NR CGI (mean±SD): 3.60 ± NR GAS (mean±SD): 40.20 ± NR ***G2:*** ***Age (mean±SD):*** 34.3 ± NR ***Males (n(%)):*** 2/15 (13.3%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 17.60 ± NR CGI (mean±SD): 4.000 ± NR GAS (mean±SD): 33.80 ± NR	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10mg/d ***Intervals:*** BID ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 6mg/d ***Intervals:*** BID

Table 54. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smulevich et al. 2005[138]	***Study design***: RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM–IV ***Study period:*** NR ***Number of centers:*** Multicenter ***Setting:*** Mixed ***Country:*** International ***Financial support:*** Industry (Johnson & Johnson) ***Washout period performed:*** yes (3 days) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** bipolar I disorder; Hx of at least one documented manic or mixed episode; met DSM–IV criteria for a current manic episode. ***Main exclusion criteria:*** Schizoaffective disorder; rapid cycling bipolar disorder; borderline or antisocial personality disorder; recent substance abuse or dependence; poor antimanic response to antipsychotic monotherapy	***G1:*** ***Age (mean±SD):*** 38.50 ± 12.20 ***Males (n(%)):*** 83/154 (53.9%) ***Ethnicity:*** Caucasian 95/154 (65.9%) ***BL symptom scores:*** BPRS (mean±SD): 32.50 ± 7.30 CGI-S (mean±SD): 3.70 ± 0.80 YMRS (mean±SD): 31.30 ± 6.50 ***G2:*** ***Age (mean±SD):*** 41.30 ± 13.10 ***Males (n(%)):*** 78/144 (54.2%) ***Ethnicity:*** Caucasian 102/154 (66.2%) ***BL symptom scores:*** BPRS (mean±SD): 32.30 ± 7.80 CGI-S (mean±SD): 3.80 ± 0.80 YMRS (mean±SD): 32.10 ± 6.90	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 2–12mg/d ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Risperidone ***Dosage:*** 1–6mg/d ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; ; CGI = Clinical Global Impression; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; GAS = Global Assessment Scale; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 55. Patient characteristics–haloperidol versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Vieta et al. 2005[32]	***Study design:*** RCT ***Registration #:*** NR ***Study population:*** Bipolar ***DSM Classification:*** DSM IV ***Study period:*** NR ***Number of centers:*** Multicenter (n = 76) ***Setting:*** Inpatient ***Country:*** Spain ***Financial support:*** Industry (Bristol–Myers Squibb, Otsuka) ***Washout period performed:*** yes (1–3 days) ***Run-in phase performed:*** no ***Followup period:*** 12 wks	***Main inclusion criteria:*** DSM–IV Dx of bipolar I disorder ***Main exclusion criteria:*** Presence of rapid–cycling bipolar I disorder; duration of the current manic episode of more than 4 weeks; proven substance misuse; pts considered unresponsive to antipsychotics; recent Tx with a long–acting antipsychotic, lithium or divalproate	***G1:*** ***Age (mean±SD):*** 41.00 ± 11.80 ***Males (n(%)):*** 57/172 (31.9%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 4.90 ± 1.31 YMRS (mean±SD): 31.50 ± 7.87 ***G2:*** ***Age (mean±SD):*** 40.80±10.80 ***Males (n(%)):*** 244/336 (72.6%) ***Ethnicity:*** NR ***BL symptom scores:*** BPRS (mean±SD): 5.00 ± 1.32 YMRS (mean±SD): 31.10 ±6.61	***G1:*** ***Classification:*** FGA ***Drug:*** Haloperidol ***Dosage:*** 10–15mg ***Intervals:*** NR ***G2:*** ***Classification:*** SGA ***Drug:*** Aripiprazole ***Dosage:*** 15–30mg ***Intervals:*** NR

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Appendix I. Patient Flow Through Trials

A) Schizophrenia and Related Psychoses

Table 56. Patient flow through trials–chlorpromazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Chiu et al. 1976[152]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–300mg/d	50–300mg/d				
	No screened:	NR					
	No randomized:	33	31				
	No completed:	14	22				
	No analyzed (E):	NR	NR				
	No analyzed (S):	14	22				
Claghorn et al. 1987[63]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50mg–1800mg/d	25mg–900mg/d				
	No screened:	NR					
	No randomized:	76	75				
	No completed:	40	48				
	No analyzed (E):	76	75				
	No analyzed (S):	76	75				
Ekblom et al. 1974[153]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	65–700mg/d	65–600mg/d				
	No screened:	NR					
	No randomized:	21	20				
	No completed:	19	17				
	No analyzed (E):	21	20				
	No analyzed (S):	21	20				

Table 56. Patient flow through trials–chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Gelenberg et al. 1979[154]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1800mg/d	25–900mg/d				
	No screened:	NR					
	No randomized:	8	7				
	No completed:	NR	NR				
	No analyzed (E):	8	7				
	No analyzed (S):	NR	6				
Guirguis et al. 1977[160]	***Classification***	FGA	SGA				
	Medication	chlorpromazine	Clozapine				
	Dosage	150–900mg/d	75–450mg/d				
	No screened:	NR					
	No randomized:	28	22				
	No completed:	19	16				
	No analyzed (E):	19	16				
	No analyzed (S):	19	16				
Hong et al. 1997[87]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1800mg/d	25–900mg/d				
	No screened:	NR					
	No randomized:	19	21				
	No completed:	17	19				
	No analyzed (E):	19	21				
	No analyzed (S):	19	21				
Kane et al. 1988[94]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	1000–1800mg/d	500–900mg/d				
	No screened:	NR					
	No randomized:	142	126				
	No completed:	124	111				
	No analyzed (E):	139	126				
	No analyzed (S):	142	126				

Table 56. Patient flow through trials–chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Leon et al. 1979[156]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	100–1600mg/d	100–1600mg/d				
	No screened:	NR					
	No randomized:	25	25				
	No completed:	17	14				
	No analyzed (E):	25	25				
	No analyzed (S):	25	25				
Lieberman et al. 2003[109]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	max of 600 mg/d	max of 400 mg/d				
	No screened:	2708					
	No randomized:	83	81				
	No completed:	62	68				
	No analyzed (E):	80	80				
	No analyzed (S):	80	80				
Rinieris et al. 1980[157]	***Classification***	FGA	FGA	SGA			
	Medication	Chlorpromazine	Trifluoperazine	Clozapine			
	Dosage	50–100mg	2.5–5mg	50–100mg			
	No screened:	NR					
	No randomized:	16	20	5			
	No completed:	10	9	5			
	No analyzed (E):	10	9	5			
	No analyzed (S):	10	9	5			
Shopsin et al. 1979[158]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1600mg/d	25–900mg/d				
	No screened:	50					
	No randomized:	12	13				
	No completed:	12	13				
	No analyzed (E):	12	13				
	No analyzed (S):	12	13				

Table 56. Patient flow through trials–chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Singer et al. 1974[161]	***Classification***	FGA	SGA				
	Medication	chlorpromazine	Clozapine				
	Dosage	50–600mg/d	50–600mg/d				
	No screened:	NR					
	No randomized:	20	20				
	No completed:	19	19				
	No analyzed (E):	19	19				
	No analyzed (S):	19	19				

d = day; E = efficacy; FGA = first-generation antipsychotic; max = maximum; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 57. Patient flow through trials–chlorpromazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 1998[66]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Olanzapine				
	Dosage	600–1200mg/d	12.5–25mg/d				
	No screened:	103					
	No randomized:	42	42				
	No completed:	29	30				
	No analyzed (E):	42	42				
	No analyzed (S):	42	42				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 58. Patient flow through trials–chlorpromazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Peuskens et al. 1997[121]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Quetiapine				
	Dosage	75–750mg/d	75–750mg/d				
	No screened:	NR					
	No randomized:	100	101				
	No completed:	64	70				
	No analyzed (E):	100	101				
	No analyzed (S):	100	101				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 59. Patient flow through trials–chlorpromazine versus ziprasidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2006[96]	***Classification***	FGA	SGA				
	Medication	Chlorpromazine	Ziprasidone				
	Dosage	100–1200mg/d	40–160mg/d				
	No screened:	NR					
	No randomized:	489	154	152			
	No completed:	135	136				
	No analyzed (E):	154	152				
	No analyzed (S):	154	152				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 60. Patient flow through trials–fluphenazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Jakovljevic et al. 1999[89]	***Classification***	FGA	SGA				
	Medication	Fluphenazine	Olanzapine				
	Dosage	6–21mg/d	5–20mg/d				
	No screened:	64					
	No randomized:	30	30				
	No completed:	22	29				
	No analyzed (E):	28	27				
	No analyzed (S):	30	30				
Ljubin et al. 2000[112]	***Classification***	FGA	SGA				
	Medication	Fluphenazine	Olanzapine				
	Dosage	6–21mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	30	30				
	No completed:	8	10				
	No analyzed (E):	8	10				
	No analyzed (S):	NR	NR				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 61. Patient flow through trials – fluphenazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 2005[67]	***Classification***	FGA	SGA	SGA			
	Medication	Fluphenazine	Quetiapine	Risperidone			
	Dosage	10–15mg/d	300–500mg/d	3–5mg/d			
	No screened:	52					
	No randomized:	13	12	13			
	No completed:	4	8	8			
	No analyzed (E):	13	12	13			
	No analyzed (S):	12	12	13			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 62. Patient flow through trials – fluphenazine versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 2005[67]	***Classification***	FGA	SGA	SGA			
	Medication	Fluphenazine	Quetiapine	Risperidone			
	Dosage	10–15mg/d	300–500mg/d	3–5mg/d			
	No screened:	52					
	No randomized:	13	12	13			
	No completed:	4	8	8			
	No analyzed (E):	13	12	13			
	No analyzed (S):	12	12	13			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 63. Patient flow through trials–haloperidol versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Andrezina et al. 2006[44]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	6.5mg	9.75mg				
	No screened:	448					
	No randomized:	185	175				
	No completed:	185	175				
	No analyzed (E):	185	175				
	No analyzed (S):	183	175				
Daniel et al. 2007[74]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	6.5mg/d	9.75mg/d				
	No screened:	NR					
	No randomized:	185	175				
	No completed:	136	140				
	No analyzed (E):	151	153				
	No analyzed (S):	150	155				
de Oliveira et al. 2009[76]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	10–15mg/d	15–30mg/d				
	No screened:	NR					
	No randomized:	33	66				
	No completed:	21	53				
	No analyzed (E):	31	66				
	No analyzed (S):	31	66				
Kane et al. 2002[92]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Aripiprazole	Aripiprazole			
	Dosage	10mg/d	15mg/d	30mg/d			
	No screened:	502					
	No randomized:	104	102	102			
	No completed:	62	68	60			
	No analyzed (E):	104	102	102			
	No analyzed (S):	103	102	101			

Table 63. Patient flow through trials–haloperidol versus aripiprazole (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kasper et al. 2003[98]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	5–10mg/d	20–30mg/d				
	No screened:	1294					
	No randomized:	433	861				
	No completed:	128	367				
	No analyzed (E):	428	851				
	No analyzed (S):	428	851				
Kim et al. 2010[102]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
McCue et al. 2006[73]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Tran–Johnson et al. 2007[31]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole	
	Dosage	7.5mg/d	1mg/d	5.25mg/d	9.75mg/d	15mg/d	
	No screened:	NR					
	No randomized:	60	57	63	57	58	
	No completed:	NR	NR	NR	NR	NR	
	No analyzed (E):	57	56	62	56	58	
	No analyzed (S):	57	56	62	56	58	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 64. Patient flow through trials–haloperidol versus asenapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2010[97]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Asenapine	Asenapine			
	Dosage	4mg/d	5mg/d	10mg/d			
	No screened:	513					
	No randomized:	115	114	106			
	No completed:	65	68	70			
	No analyzed (E):	112	109	105			
	No analyzed (S):	115	111	106			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 65. Patient flow through trials–haloperidol versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Breier et al. 1994[55]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	10–30mg/d	200–600mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	20	19				
	No analyzed (E):	20	19				
	No analyzed (S):	20	19				
Citrome et al. 2001[62]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Covington et al. 2000[70]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	NR	NR				
	Patient flow through trial						
	No screened:	NR					
	No randomized:	42	40				
	No completed:	NR	NR				
	No analyzed (E):	42	40				
	No analyzed (S):	42	40				
Itoh et al. 1977[155]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	2.25–15mg/d	75–500mg/d				
	No screened:	NR					
	No randomized:	41	47				
	No completed:	NR	NR				
	No analyzed (E):	NR	NR				
	No analyzed (S):	NR	NR				

Table 65. Patient flow through trials–haloperidol versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2001[95]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	5–16mg/d	12.5–800mg/d				
	No screened:	NR					
	No randomized:	34	37				
	No completed:	12	24				
	No analyzed (E):	11	23				
	No analyzed (S):	34	37				
Kleiser et al. 1994[103]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	16mg/d	350mg/d				
	No screened:	NR					
	No randomized:	18	18				
	No completed:	17	17				
	No analyzed (E):	17	17				
	No analyzed (S):	17	17				
Krakowski et al. 2006[105]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Clozapine	Olanzapine			
	Dosage	10–30mg/d	200–800mg/d	10–35mg/d			
	No screened:	134					
	No randomized:	36	37	37			
	No completed:	20	24	26			
	No analyzed (E):	36	37	37			
	No analyzed (S):	36	37	37			
Rosenheck et al. 1997[126]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	5–30mg/d	100–900mg/d				
	No screened:	423					
	No randomized:	218	205				
	No completed:	61	117				
	No analyzed (E):	218	205				
	No analyzed (S):	218	205				

Table 65. Patient flow through trials–haloperidol versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Volakva et al. 2002[145]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 66. Patient flow through trials–haloperidol versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Altamura et al. 2002[43]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20mg/d	10–20mg/d				
	No screened:	NR					
	No randomized:	15	13				
	No completed:	8	13				
	No analyzed (E):	11	13				
	No analyzed (S):	11	13				
Alvarez–Jimenez et al. 2006[142]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	NR					
	No randomized:	20	17	24			
	No completed:	20	17	24			
	No analyzed (E):	20	17	24			
	No analyzed (S):	20	17	24			
Beasley et al. 1996[49]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine		
	Dosage	10–20mg/d	2.5–7.5mg/d	7.5–12.5mg/d	12.5–17.5mg/d		
	No screened:	335					
	No randomized:	69	65	64	69		
	No completed:	30	30	30	34		
	No analyzed (E):	18	16	19	27		
	No analyzed (S):	69	65	64	69		
Beasley et al. 1997[50]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine	Olanzapine	
	Dosage	15±5mg/d	1.0mg/d	5±2.5mg/d	10±2.5mg/d	15±2.5mg/d	
	No screened:	NR					
	No randomized:	81	88	87	86	89	
	No completed:	43	48	48	53	55	
	No analyzed (E):	79	83	85	83	85	
	No analyzed (S):	81	88	87	86	89	

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Bernardo et al. 2001[51]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10mg/d	10mg/d				
	No screened:	NR					
	No randomized:	13	14				
	No completed:	NR	NR				
	No analyzed (E):	13	14				
	No analyzed (S):	13	14				
Boulay et al. 2007[54]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2.5–20mg/d	2.5–20mg/d				
	No screened:	NR					
	No randomized:	13	14				
	No completed:	8	14				
	No analyzed (E):	11	14				
	No analyzed (S):	11	14				
Breier et al. 2002[56]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine	Olanzapine	
	Dosage	7.5mg	2.5mg	5.0mg	7.5mg	10.0mg	
	No screened:	NR					
	No randomized:	40	48	45	46	46	
	No completed:	40	48	43	46	46	
	No analyzed (E):	40	48	43	46	46	
	No analyzed (S):	40	48	43	46	46	
Buchanan et al. 2005[58]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–30mg/d	10–30mg/d				
	No screened:	68					
	No randomized:	34	29				
	No completed:	31	26				
	No analyzed (E):	34	29				
	No analyzed (S):	34	29				

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Citrome et al. 2001[62]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Crespo–Facorro et al. 2006[71]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	202					
	No randomized:	56	55	61			
	No completed:	55	53	57			
	No analyzed (E):	56	55	61			
	No analyzed (S):	56	55	61			
Davidson et al. 2009[75]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		
de Haan et al. 2003[78]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2.5mg/d	7.5mg/d				
	No screened:	NR					
	No randomized:	12	12				
	No completed:	10	9				
	No analyzed (E):	10	9				
	No analyzed (S):	10	9				

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Goldman et al. 2004[84]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	5	5				
	No completed:	2	5				
	No analyzed (E):	5	5				
	No analyzed (S):	5	5				
Ishigooka et al. 2001[88]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	4–12mg/d	5–15mg/d				
	No screened:	NR					
	No randomized:	89	93				
	No completed:	59	75				
	No analyzed (E):	78	80				
	No analyzed (S):	84	90				
Kahn et al. 2008[91]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		
Keefe et al. 2006[101]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2–19mg/d	5–20mg/d	2–10mg/d			
	No screened:	414					
	No randomized:	97	159	158			
	No completed:	27	64	54			
	No analyzed (E):	94	153	148			
	No analyzed (S):	97	159	158			

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kim et al. 2010[102]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
Kongsakon et al. 2006[104]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg	5–20mg				
	No screened:	440					
	No randomized:	132	144				
	No completed:	94	113				
	No analyzed (E):	123	139				
	No analyzed (S):	124	139				
Krakowski et al. 2006[105]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Clozapine	Olanzapine			
	Dosage	10–30mg/d	200–800mg/d	10–35mg/d			
	No screened:	134					
	No randomized:	36	37	37			
	No completed:	20	24	26			
	No analyzed (E):	36	37	37			
	No analyzed (S):	36	37	37			
Lahti et al. 2009[106]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20mg/d	12.5–25mg/d				
	No screened:	37					
	No randomized:	14	18				
	No completed:	12	17				
	No analyzed (E):	12	17				
	No analyzed (S):	12	17				

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Lieberman et al. 2003[108]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2–20mg/d	5–20mg/d				
	No screened:	263					
	No randomized:	132	131				
	No completed:	71	89				
	No analyzed (E):	132	131				
	No analyzed (S):	132	131				
Lindenmayer et al. 2007[110]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	36					
	No randomized:	19	16				
	No completed:	19	16				
	No analyzed (E):	16	15				
	No analyzed (S):	16	15				
McCue et al. 2006[73]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Purdon et al. 2000[124]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	5–20mg/d	5–20mg/d	2–6mg/d			
	No screened:	NR					
	No randomized:	23	21	21			
	No completed:	9	12	7			
	No analyzed (E):	23	21	21			
	No analyzed (S):	23	21	21			

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Rosenheck et al. 2003[127]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	4386					
	No randomized:	150	159				
	No completed:	64	68				
	No analyzed (E):	150	159				
	No analyzed (S):	150	159				
Saddichha et al. 2008[129]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	13.4+/-3.6mg/d	16.5+/-4.6mg/d	4.4+/-1.2mg/d			
	No screened:	NR					
	No randomized:	NR	NR	NR			
	No completed:	31	35	33			
	No analyzed (E):	31	35	33			
	No analyzed (S):	NR	NR				
Sayers et al. 2005[130]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20 mg/d	10–20mg/d				
	No screened:	170					
	No randomized:	12	12				
	No completed:	7	7				
	No analyzed (E):	12	12				
	No analyzed (S):	12	12				
Sergi et al. 2007[134]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	NR					
	No randomized:	20	40	40			
	No completed:	12	22	25			
	No analyzed (E):	13	28	32			
	No analyzed (S):	13	28	32			

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Smelson et al. 2006[136]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	15	16				
	No completed:	10	8				
	No analyzed (E):	15	16				
	No analyzed (S):	NR	NR				
Smith et al. 2001[137]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–40mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	13	16				
	No analyzed (E):	13	16				
	No analyzed (S):	NR	NR				
Tollefson et al. 1997[141]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	2223					
	No randomized:	660	1336				
	No completed:	309	888				
	No analyzed (E):	660	1336				
	No analyzed (S):	660	1336				
Volakva et al. 2002[145]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Wright et al. 2001[147]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	7.5mg	10mg				
	No screened:	311					
	No randomized:	126	131				
	No completed:	126	131				
	No analyzed (E):	126	131				
	No analyzed (S):	126	131				
Wynn et al. 2007[148]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	100					
	No randomized:	11	21	19			
	No completed:	7	16	14			
	No analyzed (E):	11	21	19			
	No analyzed (S):	7	16	14			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 67. Patient flow through trials–haloperidol versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Arvanitis et al. 1997[46]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Quetiapine	Quetiapine	Quetiapine	Quetiapine	Quetiapine
	Dosage	12mg/d	75mg/d	150mg/d	300mg/d	600mg/d	750mg/d
	No screened:	402					
	No randomized:	52	53	48	52	51	54
	No completed:	18	17	21	24	27	26
	No analyzed (E):	50	52	48	51	51	53
	No analyzed (S):	52	53	48	52	51	54
Atmaca et al. 2002[47]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	10mg/d	600mg/d				
	No screened:	NR					
	No randomized:	17	18				
	No completed:	17	18				
	No analyzed (E):	17	18				
	No analyzed (S):	17	18				
Copolov et al. 2000[68]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	1–16mg/d	50–800mg/d				
	No screened:	NR					
	No randomized:	227	221				
	No completed:	147	152				
	No analyzed (E):	218	213				
	No analyzed (S):	227	221				
Davidson et al. 2009[75]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		

Table 67. Patient flow through trials–haloperidol versus quetiapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Emsley et al. 2000[79]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	5–20mg/d	600mg/d				
	No screened:	365					
	No randomized:	145	143				
	No completed:	135	127				
	No analyzed (E):	141	140				
	No analyzed (S):	141	140				
Emsley et al. 2005[80]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	5–20mg	100–800mg				
	No screened:	47					
	No randomized:	23	22				
	No completed:	15	12				
	No analyzed (E):	23	22				
	No analyzed (S):	23	22				
Glick et al. 2005[65]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	200mg/wk	500mg/d				
	No screened:	NR					
	No randomized:	14	21				
	No completed:	5	7				
	No analyzed (E):	7	15				
	No analyzed (S):	9	16				
Kahn et al. 2008[91]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		

Table 67. Patient flow through trials–haloperidol versus quetiapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
McCue et al. 2006[73]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Purdon et al. 2001[123]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	10–20mg/d	300–600mg/d				
	No screened:	NR					
	No randomized:	12	13				
	No completed:	3	9				
	No analyzed (E):	12	13				
	No analyzed (S):	12	13				
Velligan et al. 2002[143]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Quetiapine	Quetiapine			
	Dosage	12mg/d	300mg/d	600mg/d			
	No screened:	301					
	No randomized:	NR	NR	NR			
	No completed:	15	17	26			
	No analyzed (E):	15	17	26			
	No analyzed (S):	15	17	26			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 68. Patient flow through trials–haloperidol versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Apiquian et al. 2008[45]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2mg/d	1mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	6	9				
	No analyzed (E):	6	9				
	No analyzed (S):	6	9				
Blin et al. 1996[52]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–12mg/d	4–12mg/d				
	No screened:	NR					
	No randomized:	20	21				
	No completed:	14	17				
	No analyzed (E):	20	21				
	No analyzed (S):	20	21				
Borison et al. 1992[53]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–20mg/d	2–10mg/d				
	No screened:	NR					
	No randomized:	12	12				
	No completed:	NR	NR				
	No analyzed (E):	NR	NR				
	No analyzed (S):	NR	NR				
Cavallaro et al. 2001[59]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2.5–10mg/d	2.5–10mg/d				
	No screened:	NR					
	No randomized:	16	17				
	No completed:	9	10				
	No analyzed (E):	14	15				
	No analyzed (S):	14	15				

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ceskova et al. 1993[60]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–20mg/d	2–20mg/d				
	No screened:	NR					
	No randomized:	31	31				
	No completed:	28	31				
	No analyzed (E):	28	31				
	No analyzed (S):	28	31				
Chouinard et al. 1993[61]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	
	Dosage	20mg/d	2mg/d	6mg/d	10mg/d	16mg/d	
	No screened:	NR					
	No randomized:	21	24	22	22	24	
	No completed:	8	7	17	14	18	
	No analyzed (E):	21	24	22	22	24	
	No analyzed (S):	21	24	22	22	24	
Citrome et al. 2001[62]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Claus et al. 1992[64]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	1–10mg/d	1–10mg/d				
	No screened:	NR					
	No randomized:	21	21				
	No completed:	16	20				
	No analyzed (E):	21	21				
	No analyzed (S):	21	21				

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Crespo–Facorro et al. 2006[71]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	202					
	No randomized:	56	55	61			
	No completed:	55	53	57			
	No analyzed (E):	56	55	61			
	No analyzed (S):	56	55	61			
Csernansky et al. 2002[72]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–20mg/d	2–8mg/d				
	No screened:	NR					
	No randomized:	188	177				
	No completed:	89	99				
	No analyzed (E):	188	177				
	No analyzed (S):	187	173				
de Sena et al. 2003[77]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–17mg/d	1–6mg/d				
	No screened:	NR					
	No randomized:	13	20				
	No completed:	12	18				
	No analyzed (E):	12	18				
	No analyzed (S):	NR	NR				
Emsley et al. 1999[81]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–10mg/d	2–10mg/d				
	No screened:	NR					
	No randomized:	84	99				
	No completed:	58	79				
	No analyzed (E):	84	98				
	No analyzed (S):	84	98				

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Fakra et al. 2008[82]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	14	11				
	No analyzed (E):	14	11				
	No analyzed (S):	14	11				
Heck et al. 2000[85]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	3–24mg/d	2–16mg/d				
	No screened:	NR					
	No randomized:	37	40				
	No completed:	22	25				
	No analyzed (E):	37	40				
	No analyzed (S):	37	40				
Kee et al. 1998[99]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	15mg/d	6mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	9	9				
	No analyzed (E):	9	9				
	No analyzed (S):	9	9				
Keefe et al. 2003[100]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2.5–10.0mg/d	2.5–10.0mg/d	2.0–8.0mg/d			
	No screened:	49					
	No randomized:	4	7	5			
	No completed:	4	7	5			
	No analyzed (E):	4	7	5			
	No analyzed (S):	NR	NR	NR			

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Keefe et al. 2006[101]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2–19mg/d	5–20mg/d	2–10mg/d			
	No screened:	414					
	No randomized:	97	159	158			
	No completed:	27	64	54			
	No analyzed (E):	94	153	148			
	No analyzed (S):	97	159	158			
Kim et al. 2010[102]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
Lee et al. 2007[107]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	7.6+/-2.6mg/d	4.1+/-0.8mg/d				
	No screened:	68					
	No randomized:	10	10				
	No completed:	10	10				
	No analyzed (E):	10	10				
	No analyzed (S):	10	10				
Lim et al. 2010[151]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–15mg	2–6mg				
	No screened:	144					
	No randomized:	62	62				
	No completed:	62	62				
	No analyzed (E):	62	62				
	No analyzed (S):	62	62				

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Liu et al. 2000[111]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	NR	NR				
	No screened:	56					
	No randomized:	28	28				
	No completed:	19	21				
	No analyzed (E):	19	19				
	No analyzed (S):	19	19				
Marder et al. 1994[114]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	
	Dosage	20mg/d	2mg/d	6mg/d	10mg/d	16mg/d	
	No screened:	388					
	No randomized:	66	63	64	65	64	
	No completed:	28	29	35	34	36	
	No analyzed (E):	64	63	63	63	61	
	No analyzed (S):	66	63	64	65	64	
Marder et al. 2003[113]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2mg TID for the first week; then 6mg HS	2mg TID for the first week; then 6mg HS				
	No screened:	110					
	No randomized:	30	33				
	No completed:	11	18				
	No analyzed (E):	11	18				
	No analyzed (S):	30	33				
McCue et al. 2006[73]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Min et al. 1993[117]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2.5–5mg/d	2.5–5mg/d				
	No screened:	35					
	No randomized:	19	16				
	No completed:	19	13				
	No analyzed (E):	19	16				
	No analyzed (S):	19	16				
Moller et al. 2008[118]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–8mg/d	2–8mg/d				
	No screened:	1372					
	No randomized:	148	148				
	No completed:	67	88				
	No analyzed (E):	146	143				
	No analyzed (S):	146	143				
Peuskens et al. 1995[120]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	Risperidone
	Dosage	10mg/d	1mg/d	4mg/d	8mg/d	12mg/d	16mg/d
	No screened:	1362					
	No randomized:	226	229	227	230	226	224
	No completed:	163	171	182	174	164	165
	No analyzed (E):	223	226	227	228	225	223
	No analyzed (S):	225	226	227	228	225	224
Purdon et al. 2000[124]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	5–20mg/d	5–20mg/d	2–6mg/d			
	No screened:	NR					
	No randomized:	23	21	21			
	No completed:	9	12	7			
	No analyzed (E):	23	21	21			
	No analyzed (S):	23	21	21			

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Remillard et al. 2008[125]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–40mg/d	2–6mg/d				
	No screened:	NR					
	No randomized:	14	14				
	No completed:	14	14				
	No analyzed (E):	14	14				
	No analyzed (S):	NR	NR				
Schooler et al. 2005[132]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	1–8mg/d	1–8mg/d				
	No screened:	NR					
	No randomized:	277	278				
	No completed:	176	161				
	No analyzed (E):	267	266				
	No analyzed (S):	276	278				
Sergi et al. 2007[134]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	NR					
	No randomized:	20	40	40			
	No completed:	12	22	25			
	No analyzed (E):	13	28	32			
	No analyzed (S):	13	28	32			
Shrivastava et al. 2000[135]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–15mg/d	2mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	50	50				
	No analyzed (E):	50	50				
	No analyzed (S):	NR	NR				

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Tamrakar et al. 2006[139]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	10–20mg/d	4–6mg/d				
	No screened:	NR					
	No randomized:	18	18				
	No completed:	18	18				
	No analyzed (E):	18	18				
	No analyzed (S):	18	18				
Volakva et al. 2002[145]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Wirshing et al. 1999[146]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	15mg/d	6mg/d				
	No screened:	NR					
	No randomized:	33	34				
	No completed:	28	28				
	No analyzed (E):	32	33				
	No analyzed (S):	32	33				
Wynn et al. 2007[148]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	100					
	No randomized:	11	21	19			
	No completed:	7	16	14			
	No analyzed (E):	11	21	19			
	No analyzed (S):	7	16	14			

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Yen et al. 2004[149]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–20mg/d	2–12mg/d				
	No screened:	41					
	No randomized:	20	21				
	No completed:	13	14				
	No analyzed (E):	20	21				
	No analyzed (S):	20	21				
Zhang et al. 2001[150]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	6mg/d	20mg/d				
	No screened:	NR					
	No randomized:	37	41				
	No completed:	33	40				
	No analyzed (E):	37	41				
	No analyzed (S):	37	41				

d = day; E = efficacy; FGA = first-generation antipsychotic; HS = half strength; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic; TID = three times daily

Table 69. Patient flow through trials–haloperidol versus ziprasidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Brook et al. 2005[57]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	IM: 2.5–10mg/d; Oral: 5–20mg/d	IM: 10–40mg/d; Oral: 40–80mg/d				
	No screened:	621					
	No randomized:	138	429				
	No completed:	91	292				
	No analyzed (E):	138	429				
	No analyzed (S):	138	429				
Corripio et al. 2005[69]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	5–20mg/d	10–40mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	10	10				
	No analyzed (E):	10	10				
	No analyzed (S):	10	10				
Davidson et al. 2009[75]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		
Goff et al. 1998[83]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Ziprasidone	Ziprasidone	Ziprasidone	Ziprasidone	
	Dosage	15mg/d	4mg/d	10mg/d	40mg/d	160mg/d	
	No screened:	NR					
	No randomized:	17	19	17	17	20	
	No completed:	9	9	6	8	12	
	No analyzed (E):	17	19	17	17	20	
	No analyzed (S):	17	19	17	17	20	

Table 69. Patient flow through trials–haloperidol versus ziprasidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Hirsch et al. 2002[86]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	5–15mg/d	80–160mg/d				
	No screened:	363					
	No randomized:	153	148				
	No completed:	64	66				
	No analyzed (E):	117	110				
	No analyzed (S):	117	110				
Kahn et al. 2008[91]	***Classification***	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		
McCue et al. 2006[73]	***Classification***	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Miceli et al. 2010[116]	***Classification***	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	7.5–10mg	20–30mg				
	No screened:	87					
	No randomized:	27	31				
	No completed:	24	25				
	No analyzed (E):	27	31				
	No analyzed (S):	27	31				

Table 69. Patient flow through trials–haloperidol versus ziprasidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Potkin et al. 2009[122]	***Classification***	FGA	SGA	SGA			
	Medication	Haloperidol	Ziprasidone	Ziprasidone			
	Dosage	5–20mg/d	80–120mg/d	80–160mg/d			
	No screened:	NR					
	No randomized:	151	221	227			
	No completed:	16	28	25			
	No analyzed (E):	47	67	72			
	No analyzed (S):	47	67	72			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 70. Patient flow through trials–perphenazine versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2007[93]	***Classification***	FGA	SGA				
	Medication	Perphenazine	Aripiprazole				
	Dosage	8–64mg/d	15–30mg/d				
	No screened:	512					
	No randomized:	146	154				
	No completed:	115	110				
	No analyzed (E):	144	150				
	No analyzed (S):	144	150				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 71. Patient flow through trials–perphenazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ascher–Svanum et al. 2008[131]	***Classification***	FGA	SGA				
	Medication	Perphenazine	Olanzapine				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	48	229				
	No completed:	48	222				
	No analyzed (E):	48	222				
	No analyzed (S):	NR	NR				
Lieberman et al. 2005[23]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 72. Patient flow through trials–perphenazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Lieberman et al. 2005[23]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 73. Patient flow through trials–perphenazine versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ascher–Svanum et al. 2008[131]	***Classification***	FGA	SGA				
	Medication	Perphenazine	Risperidone				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	48	221				
	No completed:	48	217				
	No analyzed (E):	48	217				
	No analyzed (S):	NR	NR				
Lieberman et al. 2005[23]	***Classification***	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 74. Patient flow through trials–trifluoperazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Rinieris et al. 1980[157]	***Classification***	FGA	FGA	SGA			
	Medication	Chlorpromazine	Trifluoperazine	Clozapine			
	Dosage	50–100mg	2.5–5mg	50–100mg			
	No screened:	NR					
	No randomized:	16	20	5			
	No completed:	10	9	5			
	No analyzed (E):	10	9	5			
	No analyzed (S):	10	9	5			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

B) Bipolar Disorder

Table 75. Patient flow through trials–chlorpromazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Barbini et al. 1997[48]	***Classification***	FGA	FGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	2mg/kg/d	25mg/d				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	12	15				
	No analyzed (E):	12	15				
	No analyzed (S):	12	15				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 76. Patient flow through trials–haloperidol versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Vieta et al. 2005[32]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	10-15mg/d	15-30mg/d				
	No screened:	NR					
	No randomized:	172	175				
	No completed:	50	89				
	No analyzed (E):	164	174				
	No analyzed (S):	169	175				
Young et al. 2009[33]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	5-10mg/d	15-30mg/d				
	No screened:	NR					
	No randomized:	165	167				
	No completed:	95	95				
	No analyzed (E):	161	166				
	No analyzed (S):	165	166				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 77. Patient flow through trials–haloperidol versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Moreno et al. 2007[119]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	3-15mg/d	5-20mg/d				
	No screened:	19					
	No randomized:	5	7				
	No completed:	5	7				
	No analyzed (E):	5	7				
	No analyzed (S):	5	7				
Tohen et al. 2003[140]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	3-15mg/d	5-20mg/d				
	No screened:	498					
	No randomized:	219	234				
	No completed:	116	140				
	No analyzed (E):	219	234				
	No analyzed (S):	219	234				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 78. Patient flow through trials–haloperidol versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
McIntyre et al. 2005[115]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	2-8mg/d	100-800mg/d				
	No screened:	NR					
	No randomized:	99	102				
	No completed:	54	55				
	No analyzed (E):	98	101				
	No analyzed (S):	98	101				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 79. Patient flow through trials–haloperidol versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Janicak et al. 2001[90]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2-10mg/d	1-5mg/d				
	No screened:	62					
	No randomized:	32	30				
	No completed:	13	12				
	No analyzed (E):	32	30				
	No analyzed (S):	32	30				
Sachs et al. 2002[128]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4-12 mg/d	2-6 mg/d				
	No screened:	156					
	No randomized:	53	52				
	No completed:	25	34				
	No analyzed (E):	53	52				
	No analyzed (S):	53	52				
Segal et al. 1998[133]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	10mg/d	6mg/d				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	12	13				
	No analyzed (E):	15	15				
	No analyzed (S):	15	15				
Smulevich et al. 2005[138]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2-12mg/d	1-6mg/d				
	No screened:	NR					
	No randomized:	144	154				
	No completed:	56	77				
	No analyzed (E):	144	153				
	No analyzed (S):	144	153				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 80. Patient flow through trials–haloperidol versus ziprasidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Vieta et al. 2010[144]	***Classification***	FGA	FGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	4-30mg/d	40-160mg/d				
	No screened:	540					
	No randomized:	172	178				
	No completed:	78	73				
	No analyzed (E):	171	178				
	No analyzed (S):	171	178				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

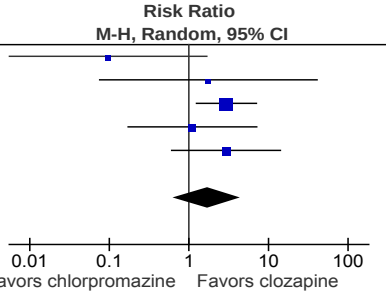
Appendix J. Forest Plots for Adverse Events

Forest plot 1. Chlorpromazine versus clozapine–Withdrawal due to adverse events

Study or Subgroup	Chlorpromazine Events	Chlorpromazine Total	Clozapine Events	Clozapine Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chiu 1976	0	31	5	33	9.6%	0.10 [0.01, 1.68]	1976
Guirguis 1977	1	28	0	16	8.1%	1.76 [0.08, 40.80]	1977
Claghorn 1987	18	76	6	75	40.6%	2.96 [1.24, 7.05]	1987
Hong 1997	2	19	2	21	18.6%	1.11 [0.17, 7.09]	1997
Lieberman 2003	6	83	2	81	23.2%	2.93 [0.61, 14.08]	2003
Total (95% CI)		**237**		**226**	**100.0%**	**1.70 [0.65, 4.45]**	
Total events	27		15				

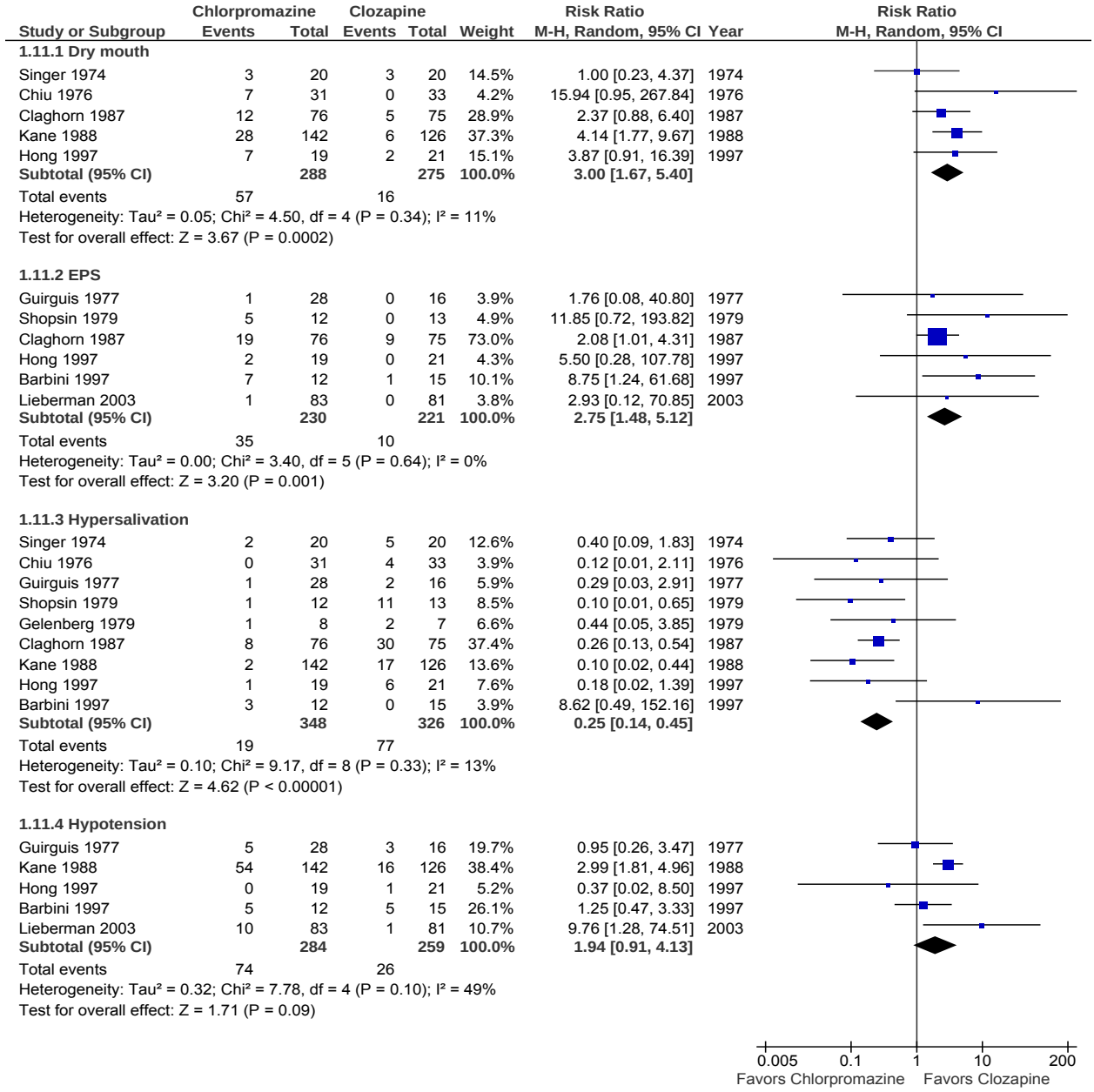
Heterogeneity: Tau² = 0.40; Chi² = 6.06, df = 4 (P = 0.19); I² = 34%

Test for overall effect: Z = 1.08 (P = 0.28)



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 2. Chlorpromazine versus clozapine–Specific adverse events

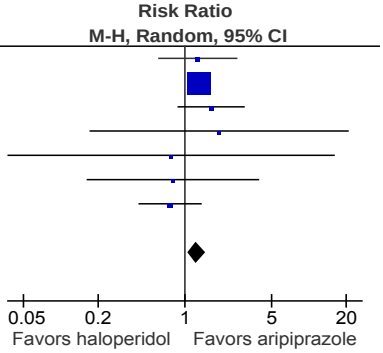


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 3. Haloperidol versus aripiprazole–Withdrawal due to adverse events

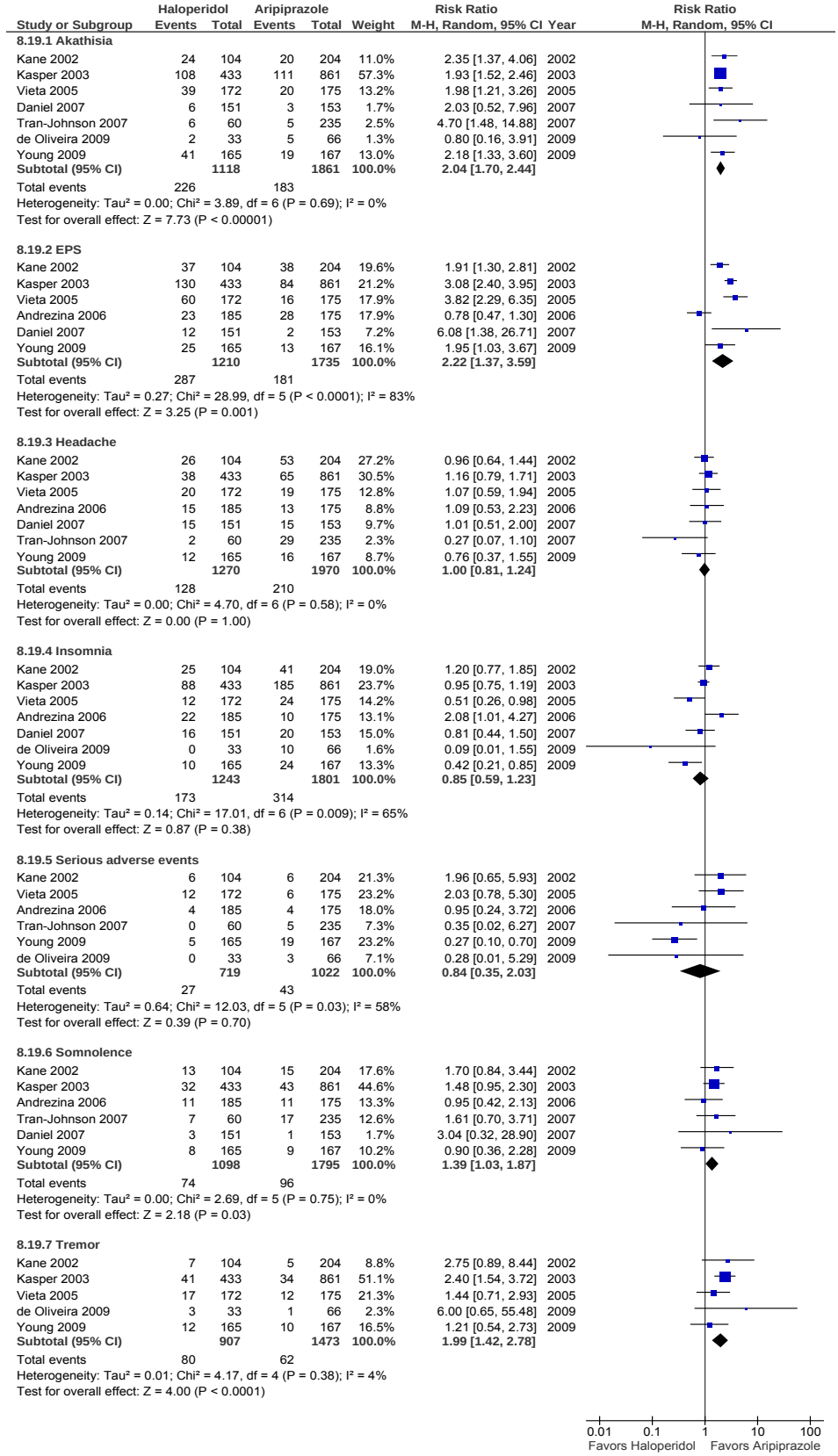
Study or Subgroup	Haloperidol Events	Haloperidol Total	Aripiprazole Events	Aripiprazole Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kane 2002	11	104	17	204	4.9%	1.27 [0.62, 2.61]	2002
Kasper 2003	138	433	213	861	78.6%	1.29 [1.08, 1.54]	2003
Vieta 2005	24	172	15	175	6.9%	1.63 [0.88, 3.00]	2005
Andrezina 2006	2	185	1	175	0.4%	1.89 [0.17, 20.68]	2006
Tran-Johnson 2007	0	60	2	235	0.3%	0.77 [0.04, 15.91]	2007
de Oliveira 2009	2	33	5	66	1.0%	0.80 [0.16, 3.91]	2009
Young 2009	18	165	24	167	7.8%	0.76 [0.43, 1.34]	2009
Total (95% CI)		**1152**		**1883**	**100.0%**	**1.25 [1.06, 1.47]**	
Total events	195		277				

Heterogeneity: Tau² = 0.00; Chi² = 4.27, df = 6 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 4. Haloperidol versus aripiprazole–Specific adverse events

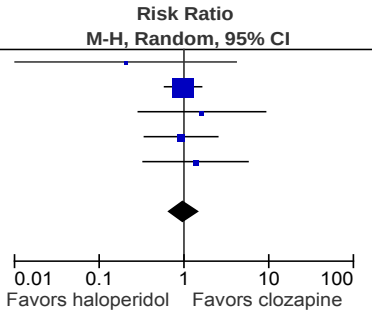


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 5. Haloperidol versus clozapine– Withdrawal due to adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Clozapine Events	Clozapine Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Breier 1994	0	37	2	38	1.9%	0.21 [0.01, 4.14]	1994
Rosenheck 1997	27	218	26	205	66.9%	0.98 [0.59, 1.62]	1997
Kane 2001	3	34	2	37	5.7%	1.63 [0.29, 9.18]	2001
Volavka 2002	6	37	7	40	17.2%	0.93 [0.34, 2.51]	2002
Krakowski 2006	4	36	3	37	8.4%	1.37 [0.33, 5.70]	2006
Total (95% CI)		**362**		**357**	**100.0%**	**1.00 [0.66, 1.50]**	
Total events	40		40				

Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

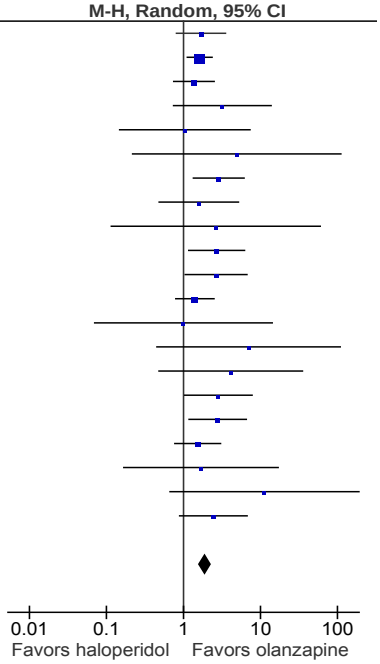


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 6. Haloperidol versus olanzapine–Withdrawal due to adverse events

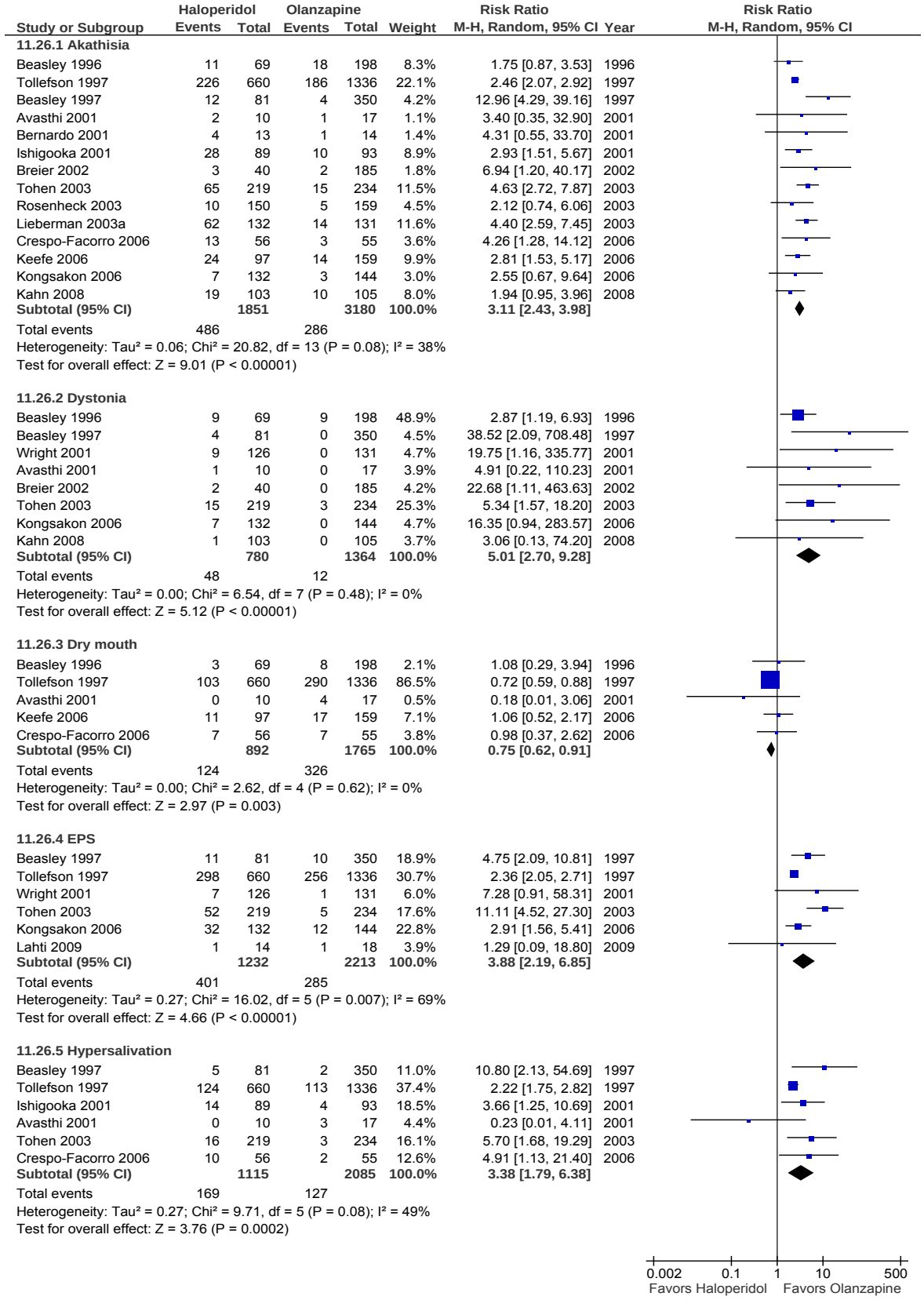
Study or Subgroup	Haloperidol Events	Haloperidol Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Beasley 1996	10	69	17	198	6.8%	1.69 [0.81, 3.51]	1996
Tollefson 1997	48	660	60	1336	26.9%	1.62 [1.12, 2.34]	1997
Beasley 1997	12	81	38	350	10.0%	1.36 [0.75, 2.49]	1997
Purdon 2000	7	23	2	21	1.7%	3.20 [0.75, 13.70]	2000
Wright 2001	2	126	2	131	1.0%	1.04 [0.15, 7.27]	2001
Avasthi 2001	1	10	0	17	0.4%	4.91 [0.22, 110.23]	2001
Ishigooka 2001	22	89	8	93	6.4%	2.87 [1.35, 6.12]	2001
Volavka 2002	6	37	4	39	2.6%	1.58 [0.48, 5.16]	2002
Altamura 2002	1	15	0	13	0.4%	2.63 [0.12, 59.40]	2002
Lieberman 2003a	19	132	7	131	5.3%	2.69 [1.17, 6.19]	2003
Rosenheck 2003	15	150	6	159	4.3%	2.65 [1.06, 6.65]	2003
Tohen 2003	25	219	19	234	11.3%	1.41 [0.80, 2.48]	2003
De Haan 2003	1	12	1	12	0.5%	1.00 [0.07, 14.21]	2003
Goldman 2004	3	5	0	5	0.5%	7.00 [0.45, 108.26]	2004
Krakowski 2006	4	36	1	37	0.8%	4.11 [0.48, 35.04]	2006
Kongsakon 2006	13	132	5	144	3.6%	2.84 [1.04, 7.74]	2006
Crespo-Facorro 2006	17	56	6	55	5.0%	2.78 [1.19, 6.53]	2006
Keefe 2006	14	97	15	159	7.8%	1.53 [0.77, 3.03]	2006
Lindenmayer 2007	2	19	1	16	0.7%	1.68 [0.17, 16.91]	2007
Boulay 2007	4	11	0	14	0.5%	11.25 [0.67, 189.01]	2007
Kahn 2008	12	103	5	105	3.6%	2.45 [0.89, 6.70]	2008
Total (95% CI)		**2082**		**3269**	**100.0%**	**1.87 [1.55, 2.27]**	
Total events	238		197				

Heterogeneity: Tau² = 0.00; Chi² = 11.99, df = 20 (P = 0.92); I² = 0%
Test for overall effect: Z = 6.45 (P < 0.00001)



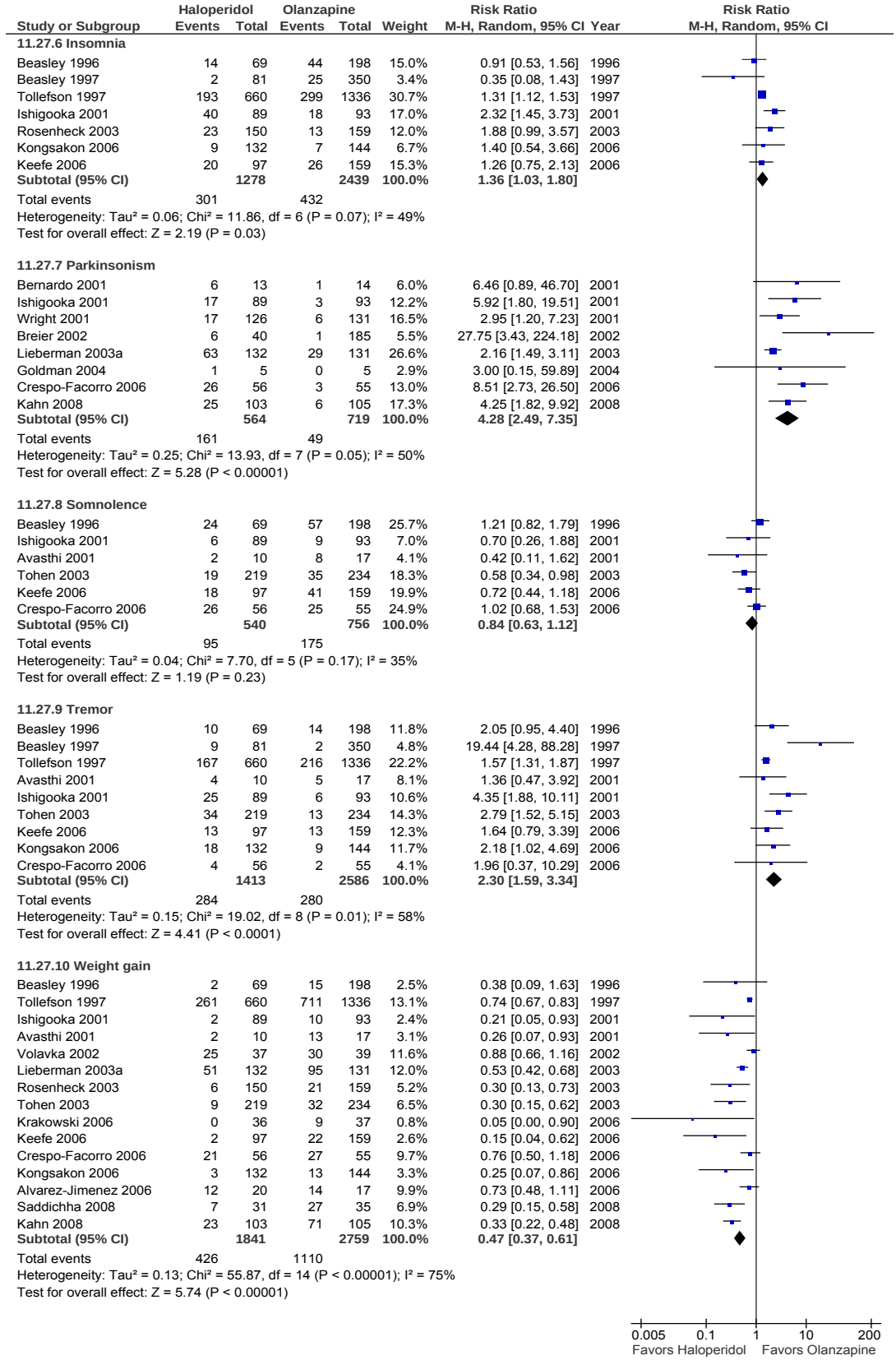
CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 7. Haloperidol versus olanzapine–Specific adverse events



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 8. Haloperidol versus olanzapine–Specific adverse events (continued)



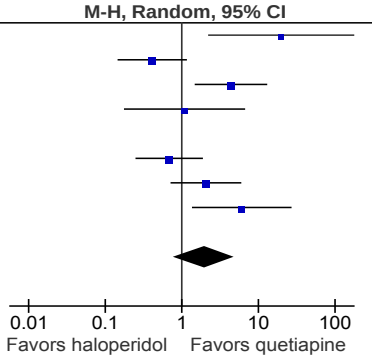
CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 9. Haloperidol versus quetiapine–Withdrawal due to adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Quetiapine Events	Quetiapine Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arvanitis 1997	4	52	1	258	9.6%	19.85 [2.26, 173.98]	1997
Emsley 2000	5	145	12	143	16.4%	0.41 [0.15, 1.14]	2000
Copolov 2000	18	227	4	221	16.1%	4.38 [1.51, 12.74]	2000
Purdon 2001	2	12	2	13	11.5%	1.08 [0.18, 6.53]	2001
Atmaca 2002	0	17	0	18		Not estimable	2002
Emsley 2005	5	23	7	22	16.6%	0.68 [0.25, 1.83]	2004
McIntyre 2005	10	99	5	102	16.3%	2.06 [0.73, 5.81]	2005
Kahn 2008	12	103	2	104	13.5%	6.06 [1.39, 26.40]	2008
Total (95% CI)		**678**		**881**	**100.0%**	**1.98 [0.79, 4.96]**	
Total events	56		33				

Heterogeneity: Tau² = 1.06; Chi² = 22.15, df = 6 (P = 0.001); I² = 73%

Test for overall effect: Z = 1.46 (P = 0.14)



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 10. Haloperidol versus quetiapine–Specific adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Quetiapine Events	Quetiapine Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
12.15.1 Akathisia							
Arvanitis 1997	8	52	3	258	13.7%	13.23 [3.63, 48.21]	1997
Copolov 2000	46	227	11	221	23.5%	4.07 [2.17, 7.65]	2000
Emsley 2000	13	145	8	143	19.9%	1.60 [0.69, 3.75]	2000
McIntyre 2005	33	99	6	102	20.3%	5.67 [2.48, 12.93]	2005
Kahn 2008	19	103	11	104	22.5%	1.74 [0.87, 3.48]	2008
Subtotal (95% CI)		**626**		**828**	**100.0%**	**3.51 [1.84, 6.72]**	
Total events	119		39				

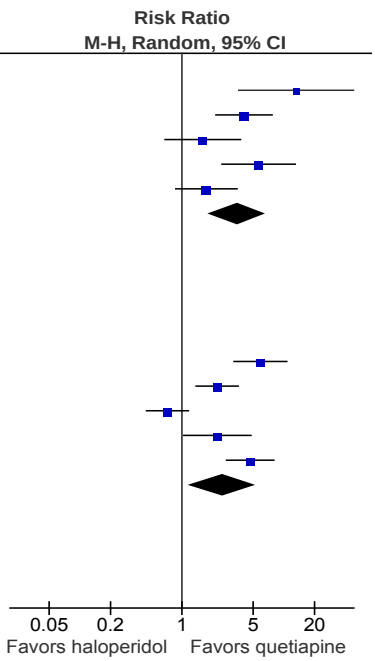
Heterogeneity: Tau² = 0.36; Chi² = 12.58, df = 4 (P = 0.01); I² = 68%

Test for overall effect: Z = 3.80 (P = 0.0001)

12.15.2 EPS							
Arvanitis 1997	19	52	16	258	19.8%	5.89 [3.25, 10.68]	1997
Emsley 2000	45	145	20	143	20.7%	2.22 [1.38, 3.56]	2000
Copolov 2000	26	227	35	221	20.7%	0.72 [0.45, 1.16]	2000
Emsley 2005	14	23	6	22	18.5%	2.23 [1.05, 4.76]	2004
McIntyre 2005	59	99	13	102	20.3%	4.68 [2.74, 7.97]	2005
Subtotal (95% CI)		**546**		**746**	**100.0%**	**2.49 [1.15, 5.39]**	
Total events	163		90				

Heterogeneity: Tau² = 0.69; Chi² = 39.54, df = 4 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.31 (P = 0.02)

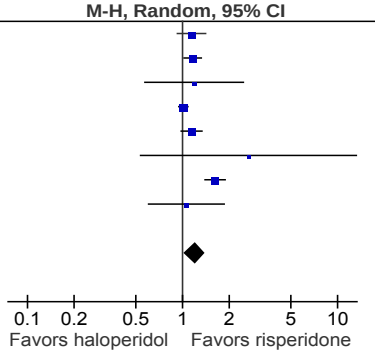


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 11. Haloperidol versus risperidone–Incidence of patients with adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Min 1993	19	19	14	16	15.5%	1.14 [0.93, 1.41]	1993
Emsley 1999	76	84	77	99	18.3%	1.16 [1.03, 1.32]	1999
Heck 2000	11	37	10	40	4.2%	1.19 [0.57, 2.47]	2000
Csernansky 2002	171	188	159	177	19.8%	1.01 [0.95, 1.08]	2002
Sachs 2002	49	53	42	52	17.4%	1.14 [0.98, 1.33]	2002
McCue 2006	5	61	2	65	1.0%	2.66 [0.54, 13.22]	2006
Smelson 2006	132	144	87	154	17.6%	1.62 [1.40, 1.88]	2006
Lim 2010	18	62	17	62	6.2%	1.06 [0.60, 1.86]	2010
Total (95% CI)		**648**		**665**	**100.0%**	**1.20 [1.01, 1.42]**	
Total events	481		408				

Heterogeneity: Tau² = 0.04; Chi² = 42.50, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 2.11 (P = 0.03)

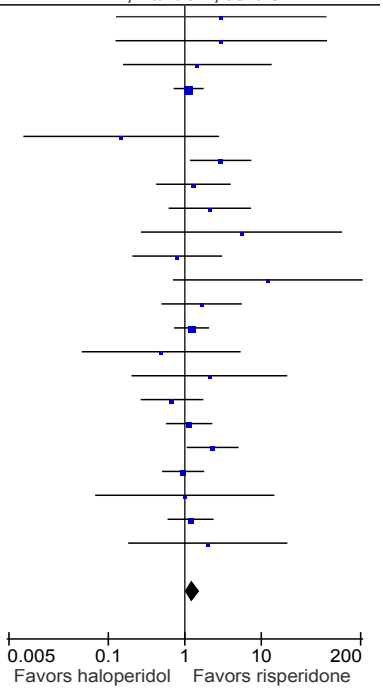


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 12. Haloperidol versus risperidone–Withdrawal due to adverse events

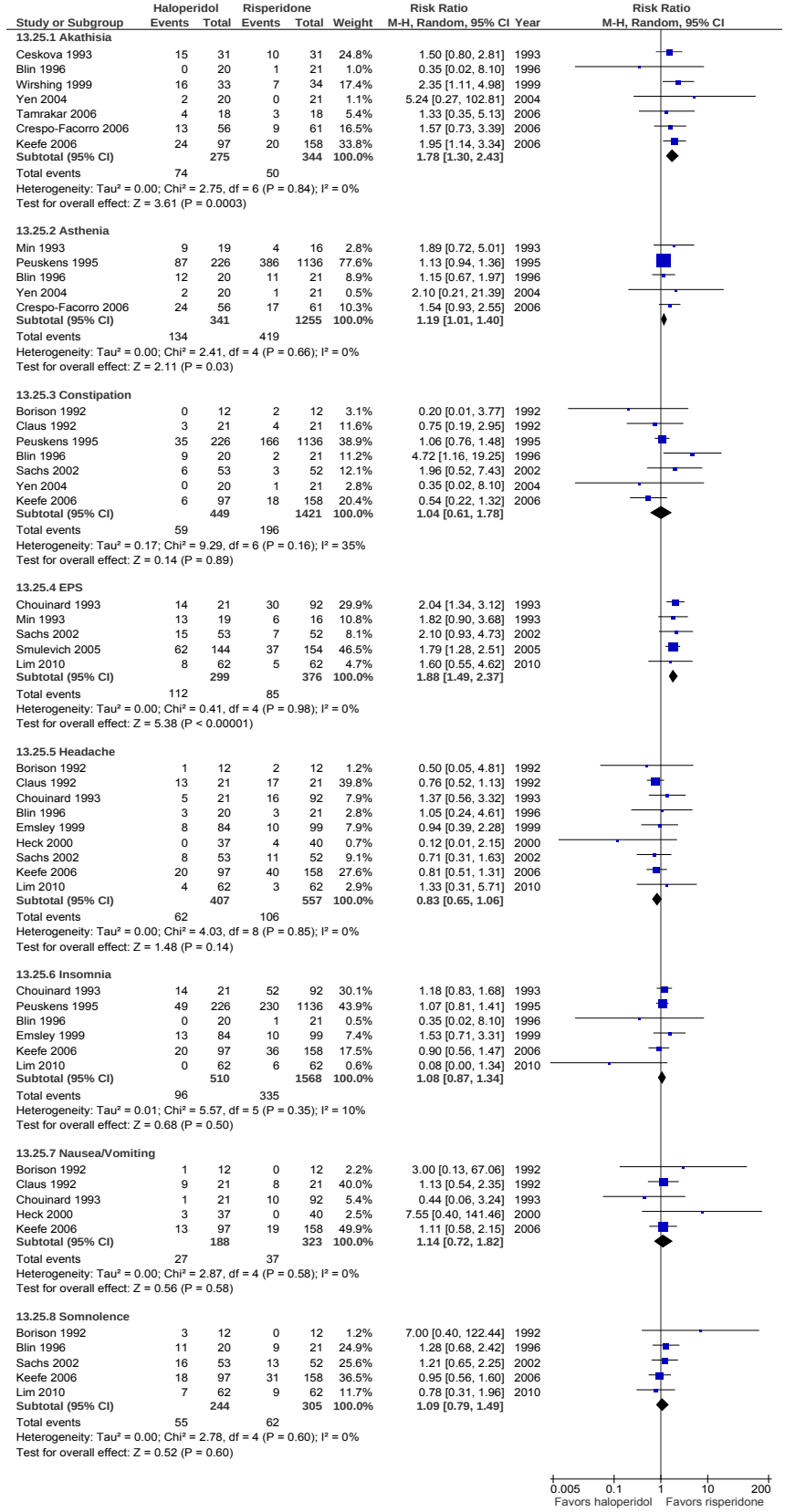
Study or Subgroup	Haloperidol Events	Haloperidol Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Claus 1992	1	21	0	21	0.4%	3.00 [0.13, 69.70]	1992
Ceskova 1993	1	31	0	31	0.4%	3.00 [0.13, 70.92]	1993
Chouinard 1993	1	21	3	92	0.8%	1.46 [0.16, 13.35]	1993
Peuskens 1995	23	226	103	1136	21.8%	1.12 [0.73, 1.72]	1995
Blin 1996	0	20	0	21		Not estimable	1996
Wirshing 1999	0	33	3	34	0.5%	0.15 [0.01, 2.74]	1999
Emsley 1999	15	84	6	99	4.9%	2.95 [1.20, 7.25]	1999
Heck 2000	6	37	5	40	3.3%	1.30 [0.43, 3.89]	2000
Purdon 2000	7	23	3	21	2.7%	2.13 [0.63, 7.19]	2000
Zhang 2001	2	37	0	41	0.4%	5.53 [0.27, 111.50]	2001
Cavallaro 2001	3	16	4	17	2.3%	0.80 [0.21, 3.02]	2001
Janicak 2001	6	32	0	30	0.5%	12.21 [0.72, 207.84]	2001
Volavka 2002	6	37	4	41	2.9%	1.66 [0.51, 5.43]	2002
Csernansky 2002	30	188	23	177	15.9%	1.23 [0.74, 2.03]	2002
Sachs 2002	1	53	2	52	0.7%	0.49 [0.05, 5.25]	2002
Yen 2004	2	20	1	21	0.7%	2.10 [0.21, 21.39]	2004
Smulevich 2005	7	144	11	154	4.7%	0.68 [0.27, 1.71]	2005
Schooler 2005	17	277	15	278	8.8%	1.14 [0.58, 2.23]	2005
Crespo-Facorro 2006	17	56	8	61	7.0%	2.31 [1.08, 4.94]	2006
Keefe 2006	14	97	24	158	10.8%	0.95 [0.52, 1.75]	2006
Fakra 2008	1	15	1	15	0.6%	1.00 [0.07, 14.55]	2008
Moller 2008	17	146	14	143	9.0%	1.19 [0.61, 2.32]	2008
Lim 2010	2	62	1	62	0.7%	2.00 [0.19, 21.49]	2010
Total (95% CI)		**1676**		**2745**	**100.0%**	**1.27 [1.04, 1.55]**	
Total events	179		231				

Heterogeneity: Tau² = 0.00; Chi² = 17.28, df = 21 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 13. Haloperidol versus risperidone–Specific adverse events

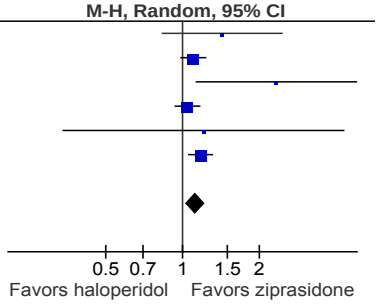


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 14. Haloperidol versus ziprasidone–Incidence of patients with adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Ziprasidone Events	Ziprasidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Goff 1998	9	17	27	73	2.6%	1.43 [0.83, 2.45]	1998
Hirsch 2002	130	153	114	148	31.4%	1.10 [0.99, 1.23]	2002
Corripio 2005	10	10	4	10	1.5%	2.33 [1.13, 4.80]	2005
Brook 2005	105	138	312	429	31.5%	1.05 [0.94, 1.17]	2005
McCue 2006	5	61	4	59	0.5%	1.21 [0.34, 4.28]	2006
Vieta 2010	149	172	131	178	32.7%	1.18 [1.06, 1.31]	2010
Total (95% CI)		**551**		**897**	**100.0%**	**1.13 [1.03, 1.23]**	
Total events	408		592				

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 5 (P = 0.20); I² = 31%
Test for overall effect: Z = 2.68 (P = 0.007)

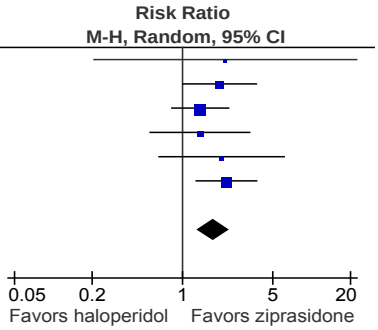


CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 15. Haloperidol versus ziprasidone–Withdrawal due to adverse events

Study or Subgroup	Haloperidol Events	Haloperidol Total	Ziprasidone Events	Ziprasidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Goff 1998	1	17	2	73	1.5%	2.15 [0.21, 22.33]	1998
Hirsch 2002	24	153	12	148	19.5%	1.93 [1.00, 3.72]	2002
Brook 2005	19	138	43	429	32.8%	1.37 [0.83, 2.28]	2005
Kahn 2008	12	103	7	82	10.6%	1.36 [0.56, 3.31]	2008
Miceli 2010	7	27	4	31	6.7%	2.01 [0.66, 6.13]	2010
Vieta 2010	36	172	17	178	28.9%	2.19 [1.28, 3.75]	2010
Total (95% CI)		**610**		**941**	**100.0%**	**1.73 [1.30, 2.32]**	
Total events	99		85				

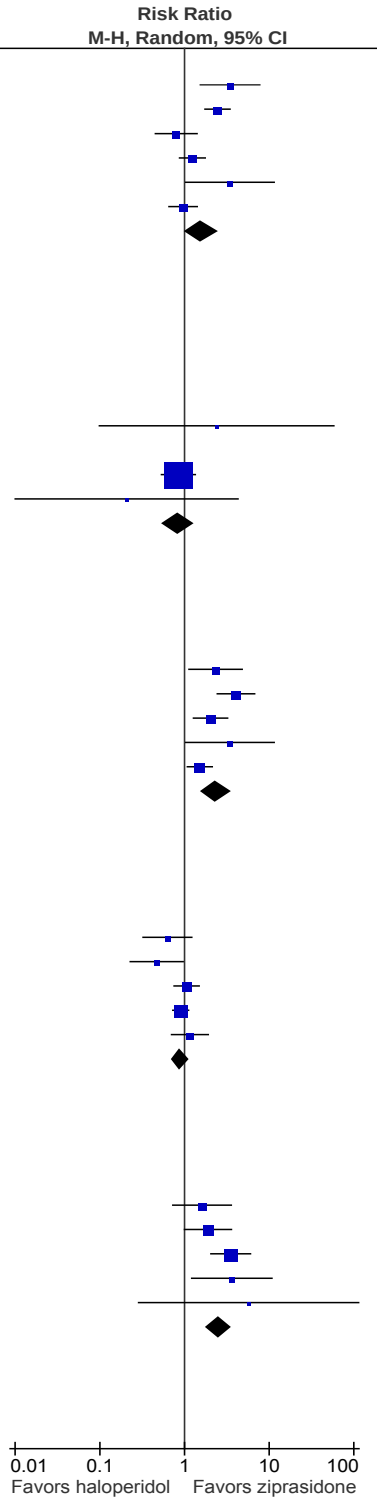
Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 16. Haloperidol versus ziprasidone–Specific adverse events

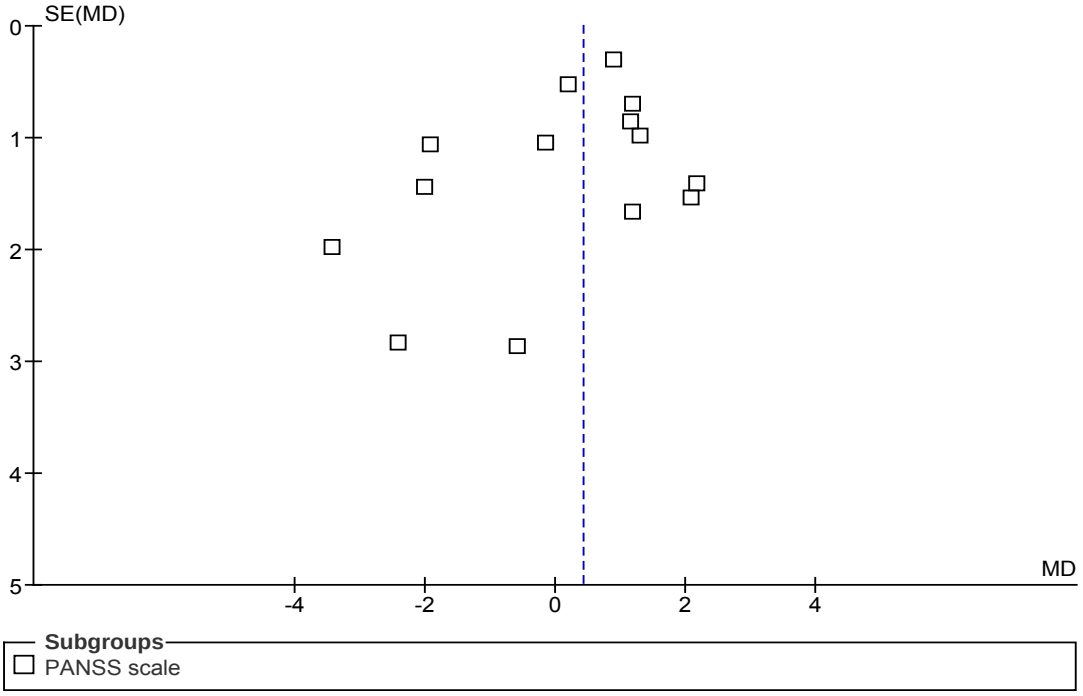
Study or Subgroup	Haloperidol Events	Haloperidol Total	Ziprasidone Events	Ziprasidone Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
14.15.1 Akathisia							
Hirsch 2002	25	153	7	148	13.4%	3.45 [1.54, 7.74]	2002
Brook 2005	45	138	57	429	20.4%	2.45 [1.75, 3.45]	2005
Kahn 2008	19	103	19	82	17.0%	0.80 [0.45, 1.40]	2008
Potkin 2009	35	151	84	448	20.3%	1.24 [0.87, 1.75]	2009
Miceli 2010	9	27	3	31	8.9%	3.44 [1.04, 11.44]	2010
Vieta 2010	39	172	42	178	19.8%	0.96 [0.66, 1.41]	2010
Subtotal (95% CI)		**744**		**1316**	**100.0%**	**1.58 [1.00, 2.50]**	
Total events	172		212				
Heterogeneity: Tau² = 0.24; Chi² = 25.16, df = 5 (P = 0.0001); I² = 80%							
Test for overall effect: Z = 1.95 (P = 0.05)							
14.15.2 ECG abnormalities							
Hirsch 2002	0	153	0	148		Not estimable	2002
Brook 2005	0	138	0	429		Not estimable	2005
Kahn 2008	1	103	0	82	2.0%	2.39 [0.10, 58.01]	2008
Potkin 2009	0	151	0	448		Not estimable	2009
Miceli 2010	14	27	19	31	95.8%	0.85 [0.53, 1.34]	2010
Vieta 2010	0	172	2	178	2.2%	0.21 [0.01, 4.28]	2010
Subtotal (95% CI)		**744**		**1316**	**100.0%**	**0.84 [0.53, 1.31]**	
Total events	15		21				
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
14.15.3 EPS							
Corripio 2005	10	10	4	10	16.7%	2.33 [1.13, 4.80]	2005
Brook 2005	30	138	23	429	22.6%	4.05 [2.44, 6.74]	2005
Potkin 2009	26	151	38	448	24.0%	2.03 [1.28, 3.23]	2009
Miceli 2010	9	27	3	31	8.7%	3.44 [1.04, 11.44]	2010
Vieta 2010	60	172	41	178	28.0%	1.51 [1.08, 2.12]	2010
Subtotal (95% CI)		**498**		**1096**	**100.0%**	**2.34 [1.56, 3.53]**	
Total events	135		109				
Heterogeneity: Tau² = 0.13; Chi² = 10.80, df = 4 (P = 0.03); I² = 63%							
Test for overall effect: Z = 4.07 (P < 0.0001)							
14.15.4 Somnolence							
Hirsch 2002	13	153	20	148	10.3%	0.63 [0.32, 1.22]	2002
Brook 2005	8	138	53	429	8.9%	0.47 [0.23, 0.96]	2005
Potkin 2009	35	151	98	448	26.0%	1.06 [0.75, 1.49]	2009
Miceli 2010	22	27	28	31	38.8%	0.90 [0.73, 1.12]	2010
Vieta 2010	28	172	25	178	16.0%	1.16 [0.71, 1.91]	2010
Subtotal (95% CI)		**641**		**1234**	**100.0%**	**0.89 [0.70, 1.12]**	
Total events	106		224				
Heterogeneity: Tau² = 0.02; Chi² = 6.28, df = 4 (P = 0.18); I² = 36%							
Test for overall effect: Z = 0.98 (P = 0.33)							
14.15.5 Tremor							
Hirsch 2002	15	153	9	148	19.1%	1.61 [0.73, 3.57]	2002
Brook 2005	14	138	23	429	29.2%	1.89 [1.00, 3.57]	2005
Potkin 2009	26	151	22	448	40.0%	3.51 [2.05, 6.00]	2009
Vieta 2010	14	172	4	178	10.3%	3.62 [1.22, 10.79]	2010
Miceli 2010	2	27	0	31	1.4%	5.71 [0.29, 114.05]	2010
Subtotal (95% CI)		**641**		**1234**	**100.0%**	**2.55 [1.79, 3.63]**	
Total events	71		58				
Heterogeneity: Tau² = 0.01; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%							
Test for overall effect: Z = 5.18 (P < 0.00001)							



CI = confidence intervals; df = degrees of freedom; I^2 = I–squared; IV = inverse variance; M-H = Mantel-Haenszel

Appendix K. Funnel Plots

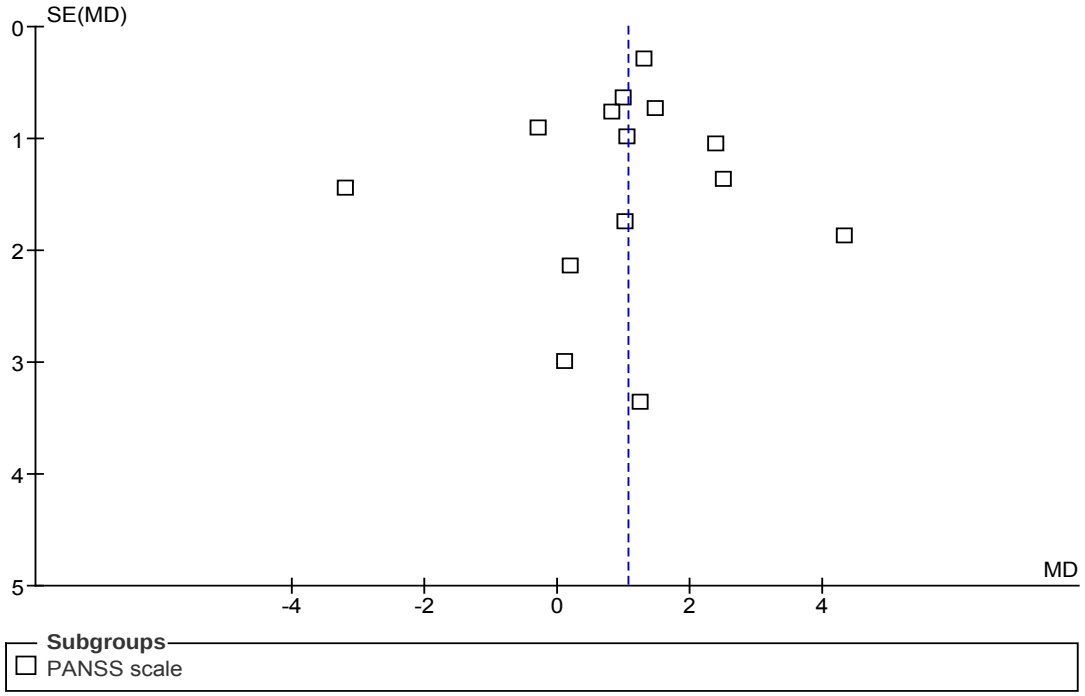
Funnel plot 1. Haloperidol versus olanzapine–Core symptoms (Sz)–Positive symptoms–PANSS (positive) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.19; Egger's regression intercept: p = 0.17

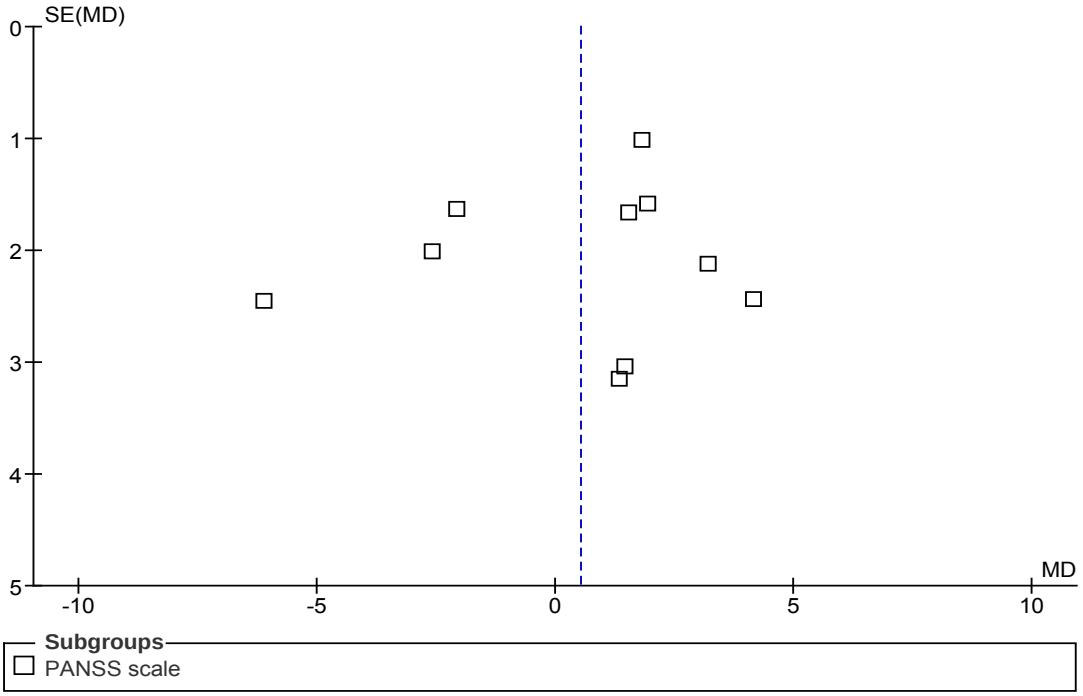
Funnel plot 2. Haloperidol versus olanzapine–Core symptoms (Sz)–Negative symptoms–PANSS (negative) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 1.00; Egger's regression intercept: p = 0.64

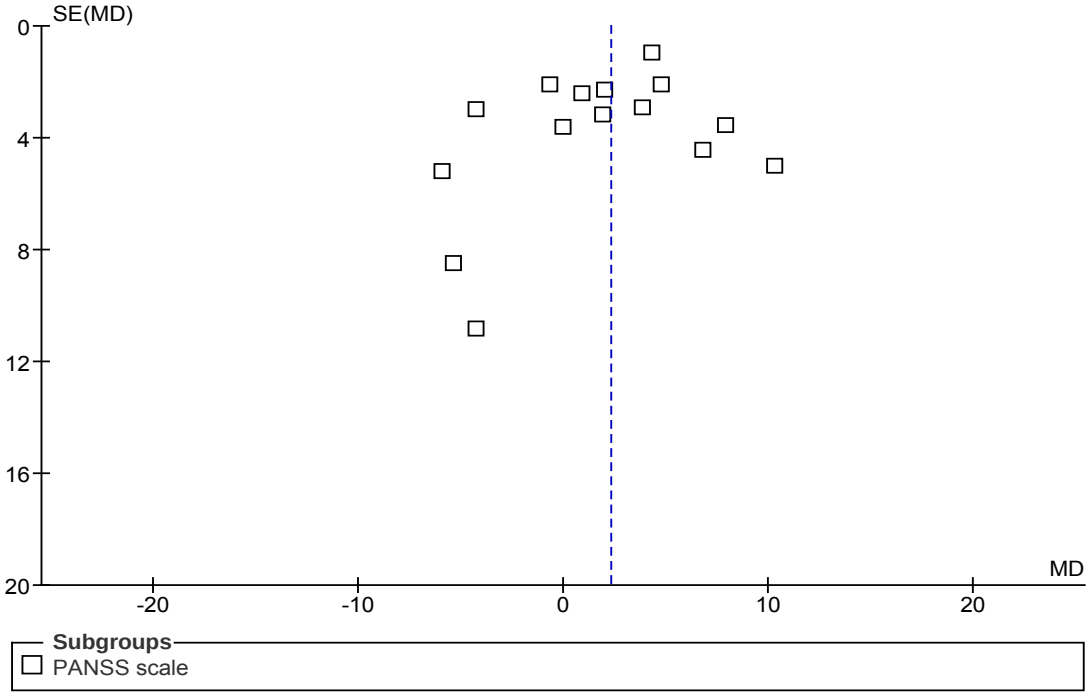
Funnel plot 3. Haloperidol versus olanzapine–Core symptoms (Sz)–General psychopathology–PANSS (general psychopathology) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.59; Egger's regression intercept: p = 0.55

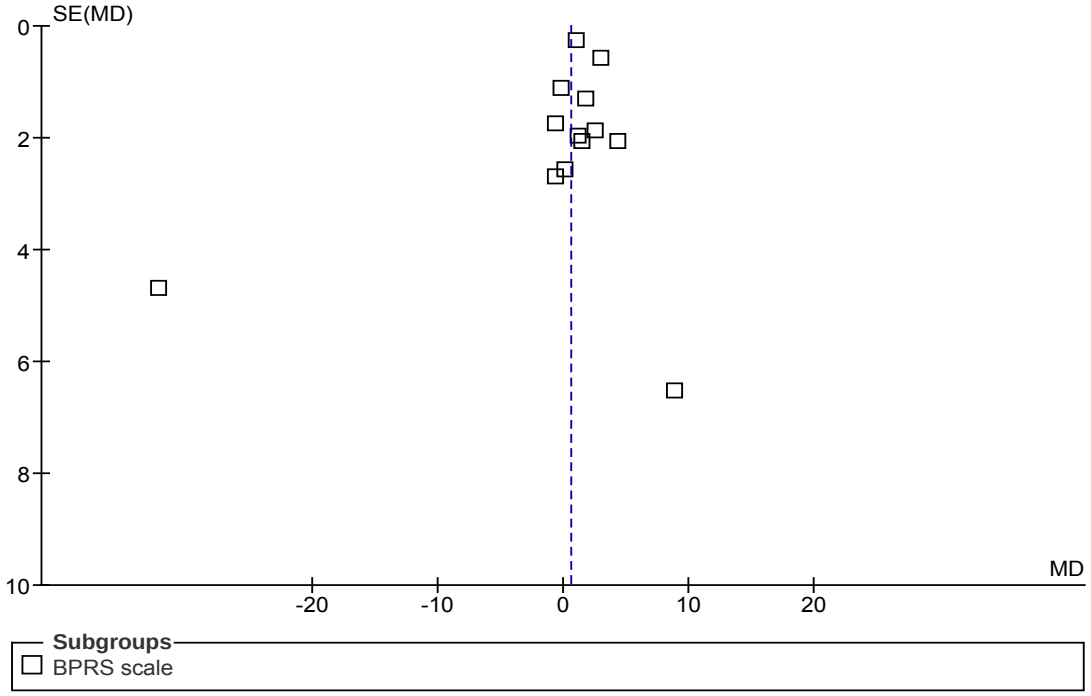
Funnel plot 4. Haloperidol versus olanzapine–Core symptoms (Sz)–Total score–PANSS scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.55; Egger's regression intercept: p = 0.24

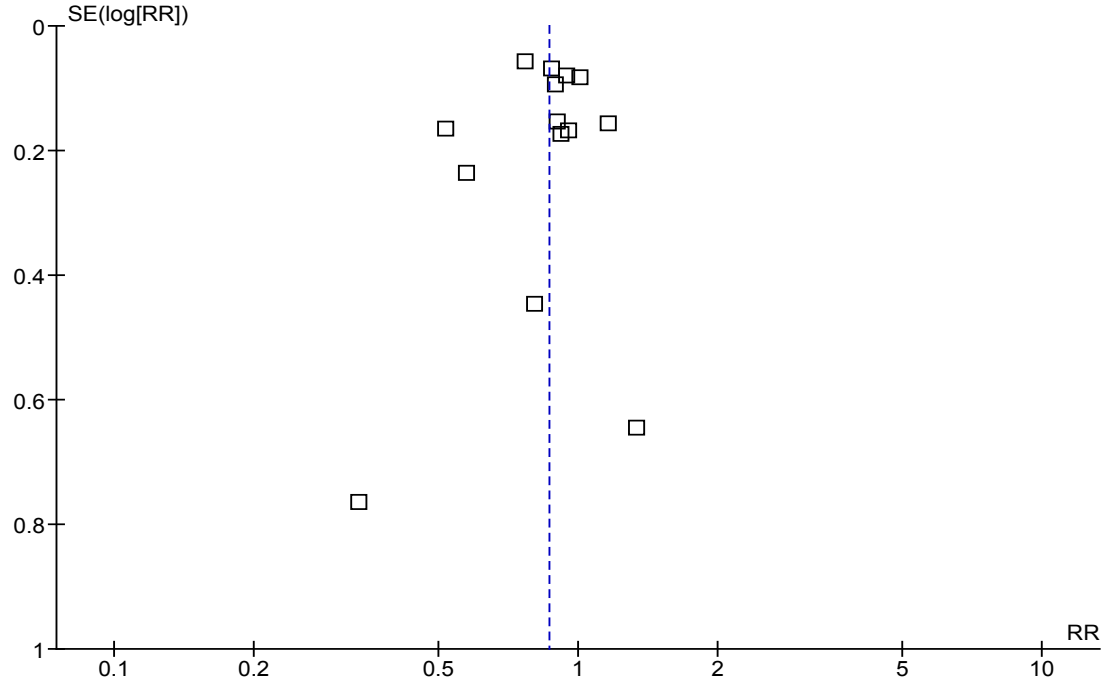
Funnel plot 5. Haloperidol versus olanzapine–Core symptoms (Sz)–Total score–BPRS scale



BPRS = Brief Psychiatric Rating Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.86; Egger's regression intercept: p = 0.49

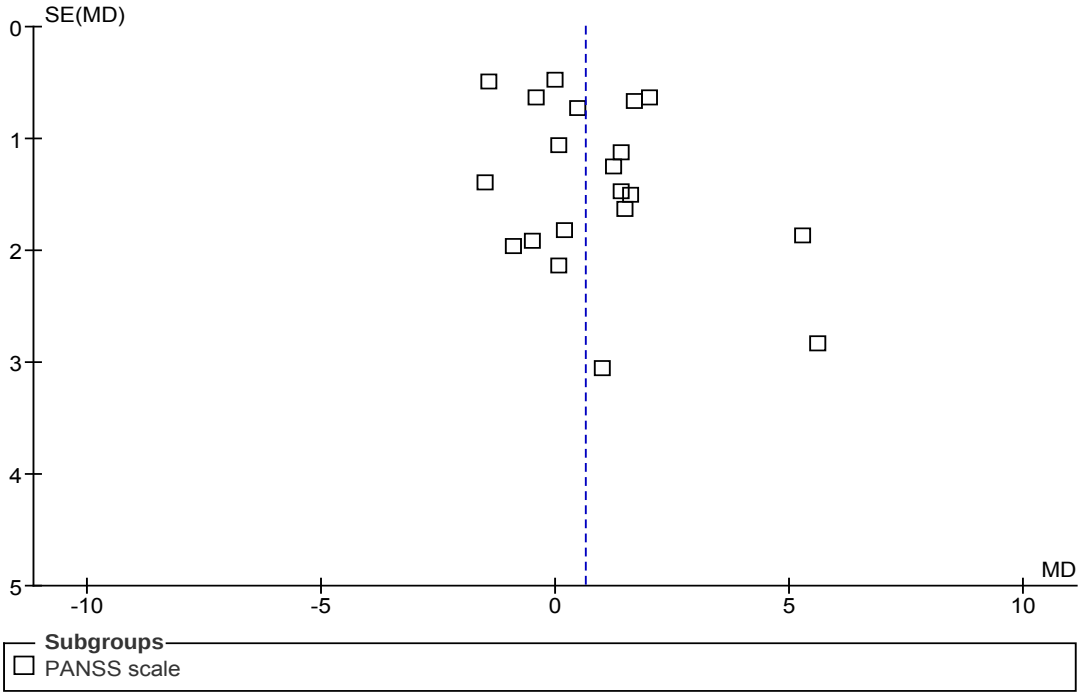
Funnel plot 6. Haloperidol versus olanzapine–response rates (Sz)



Log = Log Scale; RR = Relative Risk; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.74; Egger's regression intercept: p = 0.74

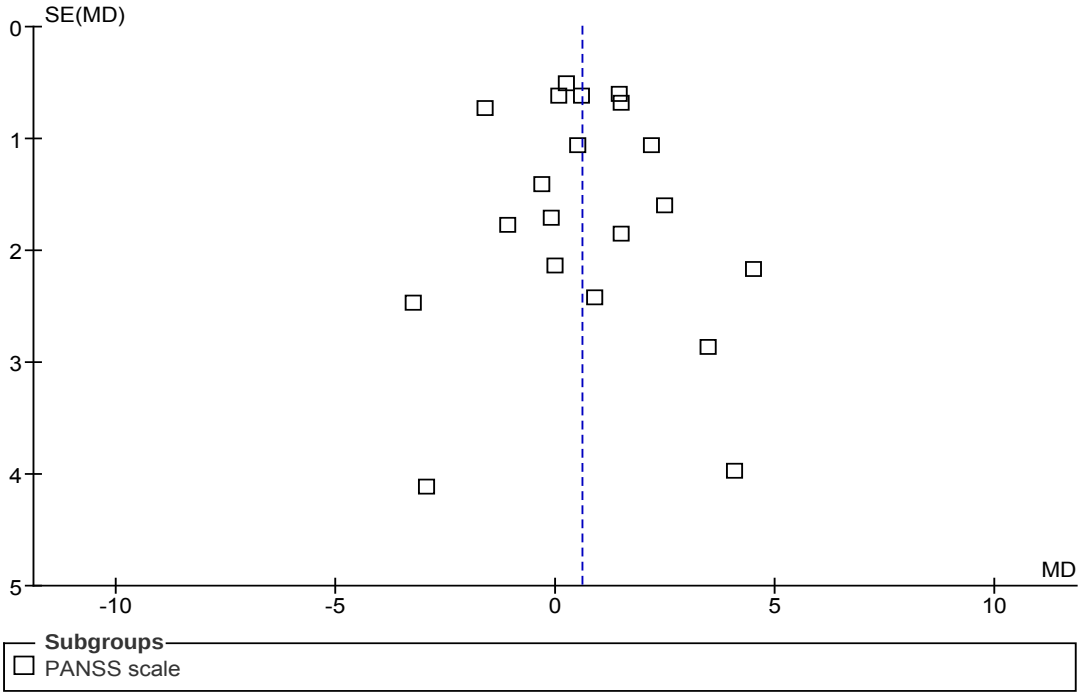
Funnel plot 7. Haloperidol versus risperidone–Core symptoms (Sz)–positive score–PANSS (positive) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.63; Egger's regression intercept: p = 0.11

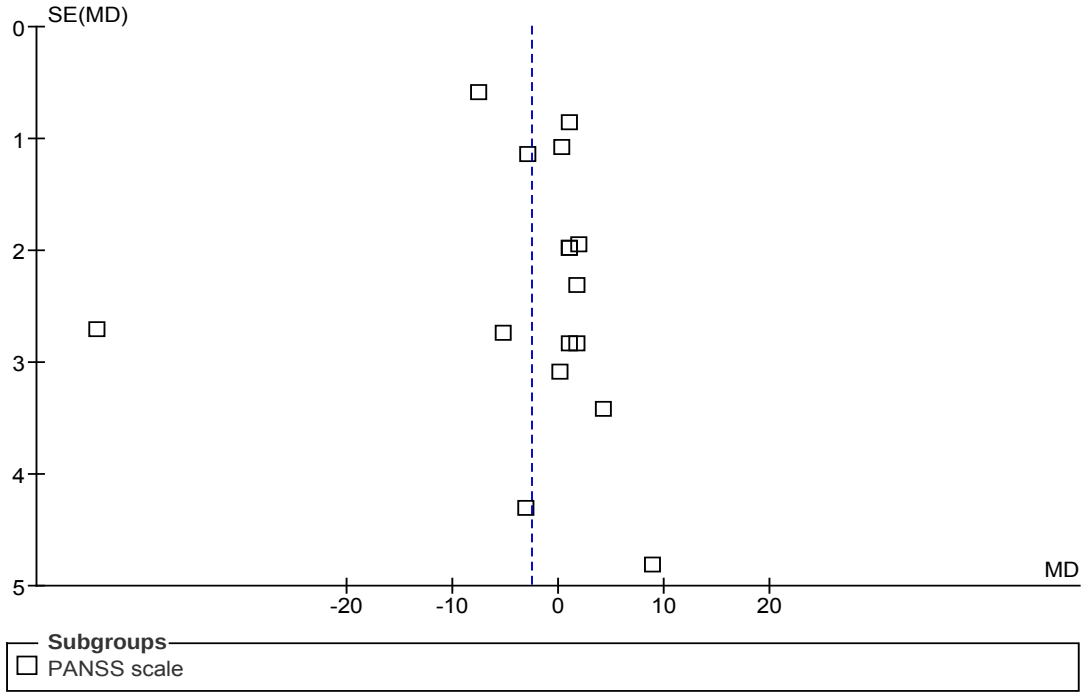
Funnel plot 8. Haloperidol versus risperidone–Core symptoms (Sz)–negative score–PANSS (negative) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.97; Egger's regression intercept: p = 0.69

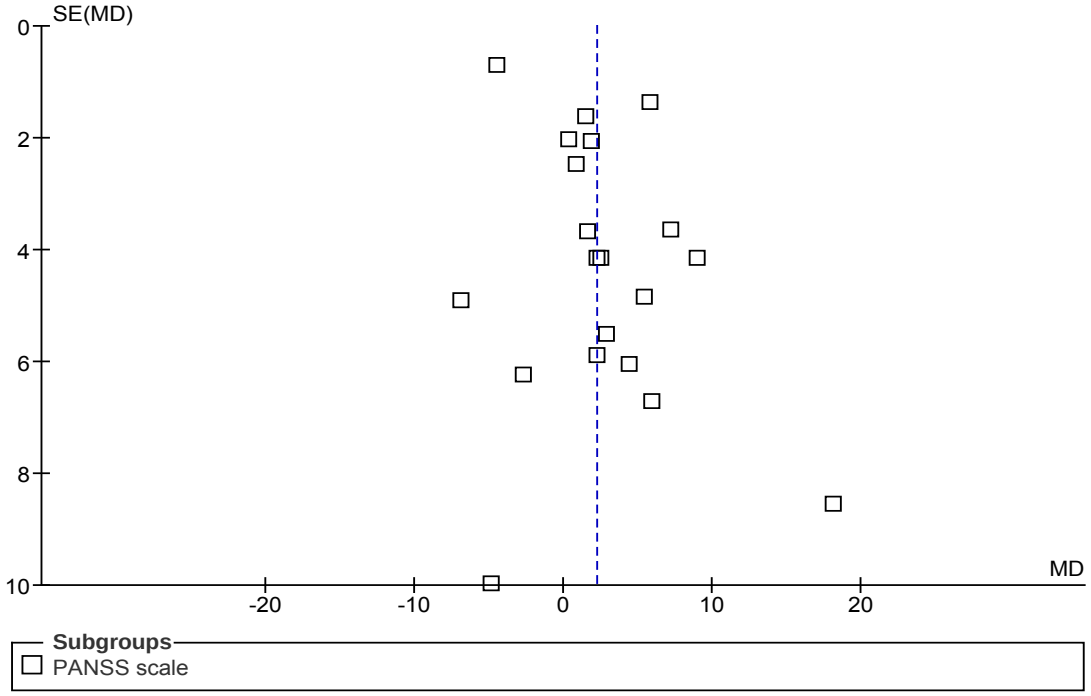
Funnel plot 9. Haloperidol versus risperidone–Core symptoms (Sz)–General symptoms–PANSS (general psychopathology) scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.26; Egger's regression intercept: p = 0.61

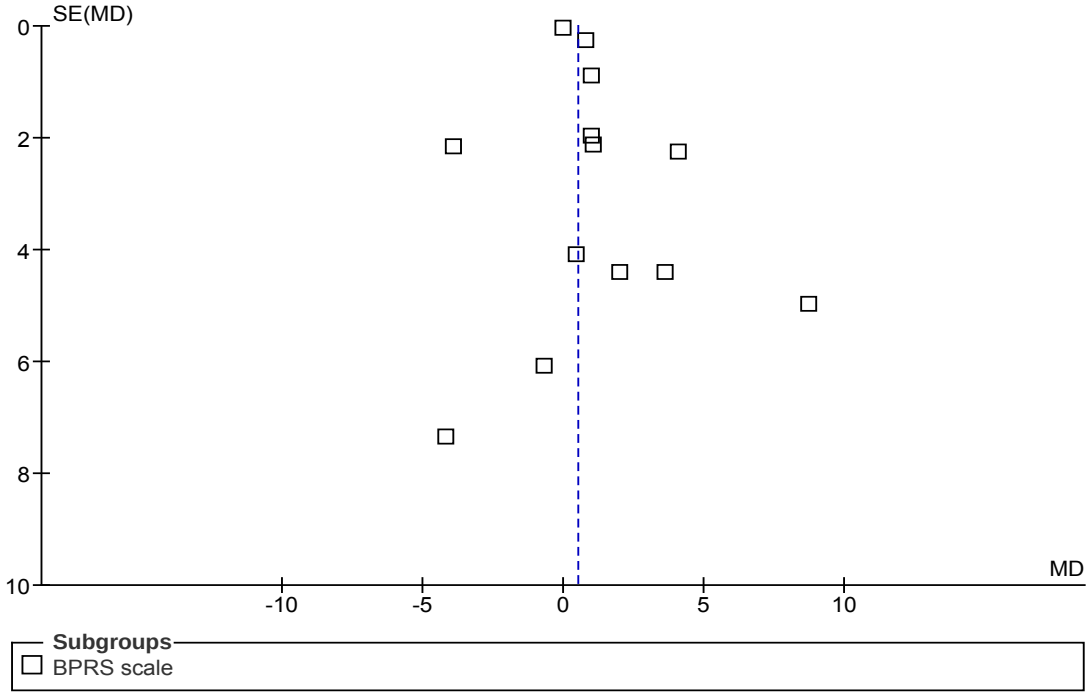
Funnel plot 10. Haloperidol versus risperidone–Core symptoms (Sz)–Total score–PANSS scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.35; Egger's regression intercept: p = 0.01

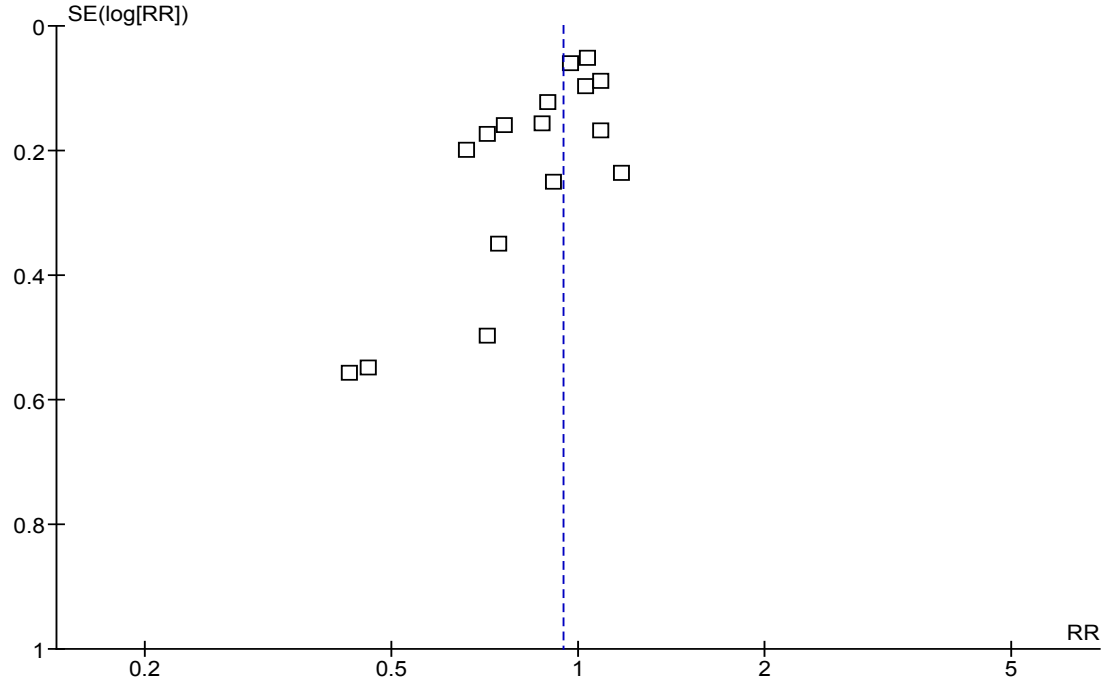
Funnel plot 11. Haloperidol versus risperidone–Core symptoms (Sz)–Total score–BPRS scale



BPRS = Brief Psychiatric Rating Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.50; Egger's regression intercept: p = 0.14

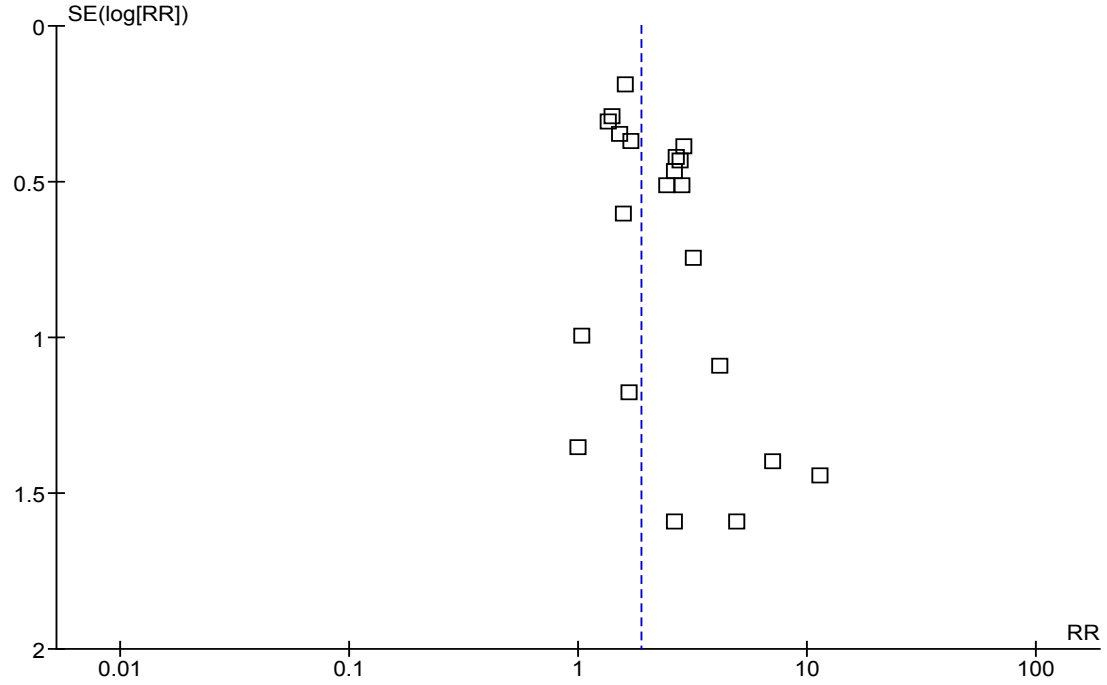
Funnel plot 12. Haloperidol versus risperidone–response rates (Sz)



Log = Log Scale; RR = Relative Risk; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: p = 0.03; Egger's regression intercept: p = 0.006

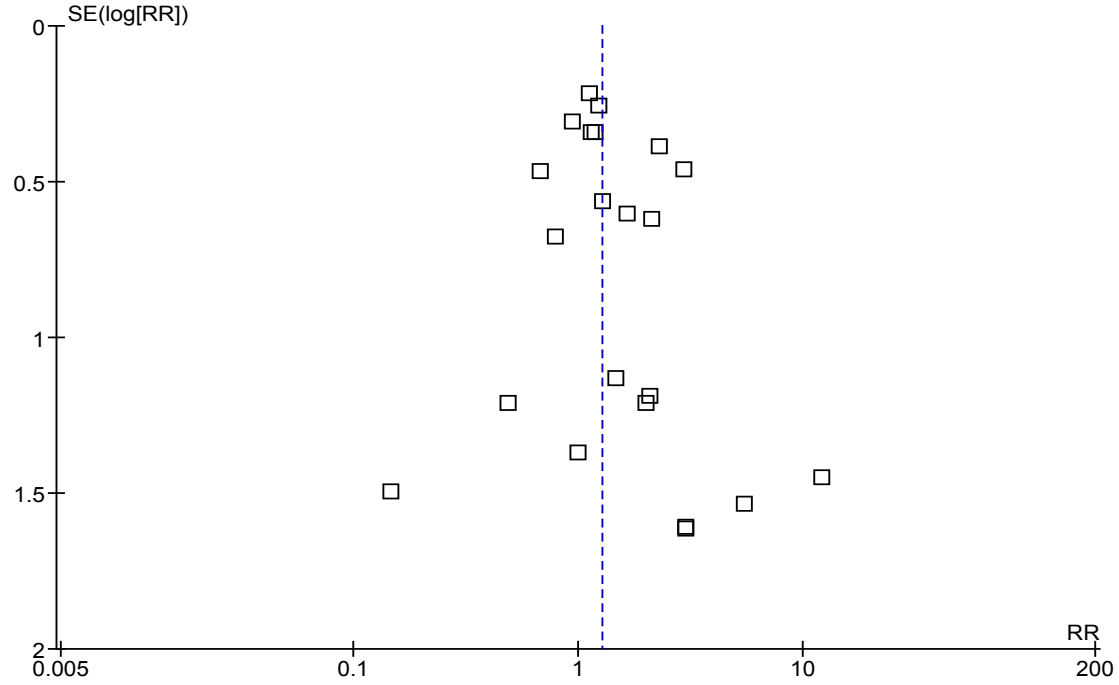
Funnel plot 13. Haloperidol versus olanzapine–withdrawals due to adverse events



Log = Log Scale; RR = Relative Risk; SE = Standard Error

Begg and Mazumdar rank correlation: p = 0.17; Egger's regression intercept: p = 0.02

Funnel plot 14. Haloperidol versus risperidone–withdrawals due to adverse events



Log = Log Scale; RR = Relative Risk; SE = Standard Error

Begg and Mazumdar rank correlation: p = 0.26; Egger's regression intercept: p = 0.28

Appendix L. Subscales, Composite Outcomes, and Functional Capacity

A) Schizophrenia and Related Psychoses

Table 81. Evidence summary table: chlorpromazine versus clozapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - cluster of four key items[94]	1	268	**3.00 (1.91, 4.09)**	NE	clozapine
BPRS - hostility subscale[63,109,154,158]	4	355	0.25 (-0.43, 0.94)	43%	ND
BPRS - psychotic subscale[152]	1	64	0.11 (-0.26, 0.48)	NE	ND
NOSIE - Irritability subscale[152]	1	64	**0.59 (0.26, 0.92)**	NE	clozapine
NOSIE - Volitional Lack/Hallucination subscale[152]	1	64	-0.09 (-0.60, 0.42)	NE	ND
Negative symptoms					
BPRS - Anergia subscale[63,109,154,160]	4	374	0.30 (-0.65, 1.25)	0%	ND
NOSIE - Depression subscale[152]	1	64	**0.81 (0.36, 1.26)**	NE	clozapine
SANS - Affective blunting subscale[109]	1	164	1.20 (0.00, 2.40)	NE	ND
SANS - Alogia subscale[109]	1	164	0.30 (-0.46, 1.06)	NE	ND
SANS - Apathy subscale[109]	1	164	-0.10 (-0.87, 0.67)	NE	ND
SANS - Avolition subscale[109]	1	164	0.50 (-0.66, 1.66)	NE	ND
SANS - Disturbance of attention subscale[109]	1	164	0.10 (-0.22, 0.42)	NE	ND
General psychopathology					
BPRS - Agitation/Activation[63,109]	2	315	-0.17 (-0.71, 0.37)	77%	ND
BPRS - Anxiety/Depression subscale[63,152]	2	215	0.07 (-0.45, 0.60)	70%	ND
BPRS - Thought Disorder[63,109,154,160]	4	374	0.26 (-0.27, 0.78)	32%	ND
NOSIE - Autistic[152]	1	64	0.39 (-0.12, 0.90)	NE	ND
NOSIE - Social competence[152,160]	2	108	0.36 (-1.10, 1.82)	89%	ND
NOSIE - Social interest[152,160]	2	108	-0.17 (-1.43, 1.10)	67%	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; I^2 = I–squared; ND = no difference; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; SANS = Scale for the Assessment of Negative Symptoms

Table 82. Evidence summary table: chlorpromazine versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - cluster of four key items[66]	1	84	1.30 (-0.28, 2.88)	NE	ND
BPRS - hostility subscale[66]	1	84	0.20 (-1.43, 1.83)	NE	ND
Negative symptoms					
BPRS - anergia[66]	1	84	0.60 (-1.05, 2.25)	NE	ND
General psychopathology					
BPRS - activation[66]	1	84	0.40 (-1.10, 1.90)	NE	ND
BPRS - anxiety/depression[66]	1	84	1.30 (-0.37, 2.97)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I^2 = I–squared; ND = no difference; NE = not estimable

Table 83. Evidence summary table: fluphenazine versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
General psychopathology					
PANSS - mood subscale[89]	1	60	1.60 (-0.32, 3.52)	NE	ND
Functional capacity					
Auditory verbal learning (# words recalled)[112]	1	18	2.30 (-1.73, 6.33)	NE	ND
Finger tapping test dominant hand[112]	1	18	34.70 (-38.87, 108.27)	NE	ND
Finger tapping test non-dominant hand[112]	1	18	47.10 (-13.64, 107.84)	NE	ND
LSEQ awakening score[89]	1	60	-2.70 (-9.76, 4.36)	NE	ND
LSEQ behavior following wakefulness[89]	1	60	-6.60 (-13.50, 0.30)	NE	ND
LSEQ getting to sleep[89]	1	60	-6.10 (-15.37, 3.17)	NE	ND
LSEQ quality of sleep[89]	1	60	-4.40 (-13.59, 4.79)	NE	ND
Serial digital learning[112]	1	18	-2.30 (-9.72, 5.12)	NE	ND
SNST color task (# of errors)[112]	1	18	-0.40 (-2.83, 2.03)	NE	ND
SNST color task (# of words)[112]	1	18	-4.50 (-50.60, 41.60)	NE	ND
SNST word task (# of errors)[112]	1	18	-1.80 (-4.97, 1.37)	NE	ND
SNST word task (# of words)[112]	1	18	6.80 (-24.02, 37.62)	NE	ND
WAIS overall function[112]	1	18	0.70 (-16.08, 17.48)	NE	ND
WCST total correct[112]	1	18	-0.50 (-27.56, 26.56)	NE	ND

I^2 = I–squared; LSEQ = Listening Self-Efficacy Questionnaire; ND = no difference; NE = not estimable; PANSS = Positive and negative symptom scale; SNST = Stroop Neuropsychological Screening Test; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test

Table 84. Evidence summary table: fluphenazine versus quetiapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - hostility subscale[67]	1	25	0.79 (-2.37, 3.95)	NE	ND
General psychopathology					
BPRS - activation[67]	1	25	-0.33 (-2.89, 2.23)	NE	ND
BPRS - anxiety/depression[67]	1	25	0.13 (-3.39, 3.65)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I^2 = I–squared; ND = no difference; NE = not estimable

Table 85. Evidence summary table: fluphenazine versus risperidone

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - hostility subscale[67]	1	26	0.92 (-2.12, 3.96)	NE	ND
General psychopathology					
BPRS - Activation subscale[67]	1	26	0.00 (-2.62, 2.62)	NE	ND
BPRS - Anxiety/depression subscale[67]	1	26	1.07 (-3.21, 5.35)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I^2 = I–squared; ND = no difference; NE = not estimable

Table 86. Evidence summary table: haloperidol versus asenapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
PANSS - hostility/excitement subscale[97]	1	335	-0.70 (-1.54, 0.14)	NE	ND
General psychopathology					
PANSS - anxiety/depression subscale[97]	1	335	0.26 (-0.51, 1.04)	NE	ND
PANSS - disorganized thought subscale[97]	1	335	0.01 (-0.95, 0.97)	NE	ND

I^2 = I–squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale

Table 87. Evidence summary table: haloperidol versus clozapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - hostile/suspiciousness subscale[95]	1	71	**1.40 (0.29, 2.51)**	NE	clozapine
BPRS - psychosis cluster subscale[95]	1	71	**2.70 (0.48, 4.92)**	NE	clozapine
PANSS - hostility subscale[62]	1	77	**0.71 (0.07, 1.35)**	NE	clozapine
PANSS - excitement factor[145]	1	77	-0.60 (-1.20, 0.00)	NE	ND
PANSS - positive factor[145]	1	77	0.06 (-0.38, 0.50)	NE	ND
Negative symptoms					
PANSS - negative factor[145]	1	77	**-0.41 (-0.80, -0.02)**	NE	haloperidol
SANS - affective flattening subscale[95]	1	71	-0.30 (-0.84, 0.24)	NE	ND
SANS - alogia subscale[95]	1	71	0.10 (-0.44, 0.64)	NE	ND
SANS - anhedonia/sociality subscale[95]	1	71	-0.30 (-0.89, 0.29)	NE	ND
SANS - avolition/apathy subscale[95]	1	71	0.20 (-0.36, 0.76)	NE	ND
General psychopathology					
BPRS - activation[95]	1	71	0.60 (-0.26, 1.46)	NE	ND
BPRS - anergia[95]	1	71	-0.70 (-2.55, 1.15)	NE	ND
BPRS - anxiety/depression[95]	1	71	1.10 (-0.65, 2.85)	NE	ND
BPRS - thought disorder[95]	1	71	0.30 (-1.68, 2.28)	NE	ND
PANSS - cognitive factor[145]	1	77	-0.03 (-0.36, 0.30)	NE	ND
PANSS - depression/anxiety factor[145]	1	77	-0.05 (-0.46, 0.36)	NE	ND
Functional capacity					
Block Design[55,105]	2	148	-0.89 (-2.44, 0.67)	80%	ND
Cat. Fluency[55]	1	75	**-11.50 (-17.71, -5.29)**	NE	clozapine
Declarative verbal learning and memory - Neurocognitive testing[145]	1	77	0.06 (-0.40, 0.52)	NE	ND
Disorientation[105]	1	73	0.19 (-0.28, 0.66)	NE	ND
Executive function[105]	1	73	0.15 (-0.12, 0.42)	NE	ND
GCI[105]	1	73	-0.07 (-0.35, 0.21)	NE	ND
General intelligence[103]	1	34	**-9.00 (-17.87, -0.13)**	NE	clozapine
Judgment of Lines[55]	1	75	-5.00 (-11.96, 1.96)	NE	ND
Memory: Figural[55]	1	75	0.17 (-0.67, 1.01)	NE	ND
Memory: Logical[55]	1	75	5.80 (-2.67, 14.27)	NE	ND
Memory: Verbal pairs[55]	1	75	-0.60 (-2.94, 1.74)	NE	ND
Memory: Visual pairs[55]	1	75	-0.90 (-3.09, 1.29)	NE	ND
Memory: Visual Reprod.[55]	1	75	-0.80 (-4.70, 3.10)	NE	ND
Motor function[105]	1	73	-0.29 (-0.60, 0.02)	NE	ND
Neurocognitive Global Score[145]	1	77	-0.19 (-0.43, 0.05)	NE	ND
Neurocognitive testing - General executive and perceptual organization[145]	1	77	-0.19 (-0.46, 0.08)	NE	ND
Neurocognitive testing - Processing speed and attention[145]	1	77	-0.29 (-0.74, 0.16)	NE	ND
Neurocognitive testing - Simple motor Functioning[145]	1	77	**-0.55 (-1.00, -0.10)**	NE	clozapine
Mooney Faces[55]	1	75	-0.80 (-1.70, 0.10)	NE	ND
MMSE[55]	1	75	-1.14 (-3.56, 1.28)	NE	ND
Poor attention[105]	1	75	0.21 (-0.25, 0.67)	NE	ND
Stroop[55]	1	75	-1.00 (-5.08, 3.08)	NE	ND
Syndrome short test[103]	1	34	**-28.70 (-31.51, -25.89)**	NE	clozapine
Trail Making Test A[105]	1	73	-0.27 (-0.78, 0.24)	NE	ND
Trail Making Test B[55]	1	75	0.00 (-0.10, 0.10)	NE	ND

Table 87. Evidence summary table: haloperidol versus clozapine (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Verbal fluency[55]	1	75	-1.50 (-7.42, 4.42)	NE	ND
Verbal Memory[105]	1	73	0.01 (-0.44, 0.46)	NE	ND
Visual Memory[105]	1	73	0.23 (-0.36, 0.82)	NE	ND
WCST[55]	1	75	0.40 (-8.02, 8.82)	NE	ND

BPRS = Brief Psychiatric Rating Scale; GCI = General Cognitive Index; I^2 = I–squared; MMSE = Mini–Mental State Examination; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; WCST = Wisconsin Card Sorting Test

Table 88. Evidence summary table: haloperidol versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - anxiety[159]	1	27	1.40 (-0.54, 3.34)	NE	ND
BPRS - hostility subscale[88]	1	182	**1.75 (1.04, 2.46)**	NE	olanzapine
PANSS - hostility subscale[62]	1	76	0.71 (-0.02, 1.44)	NE	ND
PANSS - PEC[56,147]	2	482	0.07 (-1.54, 1.67)	69%	ND
PANSS - excitement factor[145]	1	76	-0.25 (-0.81, 0.31)	NE	ND
PANSS - positive factor[145]	1	76	-0.21 (-0.66, 0.24)	NE	ND
Negative symptoms					
BPRS - activation[88]	1	182	0.74 (-0.19, 1.67)	NE	ND
BPRS - anergia[88]	1	182	0.33 (-0.60, 1.26)	NE	ND
PANSS - negative factor[145]	1	76	-0.37 (-0.74, 0.00)	NE	ND
SANS - Affective flattening subscale[159]	1	27	0.38 (-0.48, 1.24)	NE	ND
SANS - Alogia subscale[159]	1	27	0.08 (-0.84, 1.00)	NE	ND
SANS - Anhedonia subscale[159]	1	27	0.76 (-0.49, 2.01)	NE	ND
SANS - Attention subscale[159]	1	27	0.77 (-0.41, 1.95)	NE	ND
SANS - Avoilition subscale[159]	1	27	0.07 (-0.94, 1.08)	NE	ND
SANS - composite[49]	1	267	2.93 (-1.35, 7.21)	NE	ND
General psychopathology					
BPRS - Psychosis[106]	1	32	-1.10 (-2.59, 0.39)	NE	ND
BPRS - anxiety/depression[88]	1	182	0.72 (-0.28, 1.72)	NE	ND
PANSS - Cognitive factor[145]	1	76	-0.26 (-0.57, 0.05)	NE	ND
PANSS - Depression/anxiety factor[145]	1	76	-0.19 (-0.56, 0.18)	NE	ND
BPRS - thought disorder[88]	1	182	0.25 (-0.72, 1.22)	NE	ND
Subjective well-being - emotional regulation subscale[78]	1	24	1.70 (-1.07, 4.47)	NE	ND
Subjective well-being - mental functioning subscale[78]	1	24	0.80 (-2.92, 4.52)	NE	ND
Subjective well-being - physical functioning subscale[78]	1	24	1.80 (-0.62, 4.22)	NE	ND
Subjective well-being - self-control subscale[78]	1	24	**3.20 (0.75, 5.65)**	NE	olanzapine
Functional capacity					
Attention Span[124]	1	44	-0.22 (-0.59, 0.15)	NE	ND
Block Design[105]	1	73	**-0.61 (-1.15, -0.07)**	NE	olanzapine
Brief test of attention (correct responses)[71]	1	111	-0.76 (-1.88, 0.36)	NE	ND
COWAT, category/semantic[110]	1	35	-5.13 (-10.50, 0.24)	NE	ND
continuous performance test (correct responses)[71]	1	111	-2.78 (-7.30, 1.74)	NE	ND
Cognitive composite score[75]	1	208	-0.10 (-0.28, 0.08)	NE	ND
COWAT[71,110,124,134]	4	250	-2.64 (-8.48, 3.19)	78%	ND
CRT[54]	1	25	-50.00 (-163.48, 63.48)	NE	ND
CVLT[134]	1	60	4.60 (-1.91, 11.11)	NE	ND
D2 Test of Attention[54]	1	25	-1.71 (-37.40, 33.98)	NE	ND
Declarative verbal learning and memory[145]	1	76	-0.34 (-0.74, 0.06)	NE	ND
Design List Learning[124]	1	44	**-4.68 (-9.30, -0.06)**	NE	olanzapine
Digit Span[124]	1	44	-0.70 (-2.80, 1.40)	NE	ND
Digit Span Backward[54]	1	25	0.82 (-0.82, 2.46)	NE	ND
Digit Span Distractibility Test[54]	1	25	7.99 (-13.85, 29.83)	NE	ND
Digit Symbol Subtest[124]	1	44	-4.20 (-9.76, 1.36)	NE	ND
Discrimination of self-generated words[101]	1	256	0.07 (-0.06, 0.20)	NE	ND
Disorientation[105]	1	73	-0.41 (-0.87, 0.05)	NE	ND
Distractibility task, no. correct[110]	1	35	-2.33 (-7.97, 3.31)	NE	ND

Table 88. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
DSC CPT[134]	1	60	0.05 (-0.01, 0.11)	NE	ND
DSC[134]	1	60	2.60 (-4.01, 9.21)	NE	ND
Executive function[105]	1	73	-0.03 (-0.29, 0.23)	NE	ND
Executive Skills[124]	1	44	-0.33 (-0.96, 0.30)	NE	ND
Fagerstrom Tolerance Questionnaire[102]	1	67	**2.60 (1.52, 3.68)**	NE	haloperidol
Finger Tapping[54,124]	2	69	-4.02 (-10.66, 2.62)	36%	ND
Finger tapping left, no. taps[110]	1	35	-8.43 (-16.57, -0.29)	NE	ND
Finger tapping right, no. taps[110]	1	35	-7.59 (-18.35, 3.17)	NE	ND
Finger tapping test (mean taps/10 ses)[71]	1	111	0.27 (-3.15, 3.69)	NE	ND
GCI[105]	1	73	**-0.49 (-0.77, -0.21)**	NE	olanzapine
General executive and perceptual organization - Neurocognitive testing[145]	1	76	**-0.45 (-0.76, -0.14)**	NE	olanzapine
GPT[134]	1	60	-14.80 (-42.36, 12.76)	NE	ND
Pegboard[54,71,75,124]	4	388	3.14 (-2.03, 8.31)	76%	ND
Hooper Visual Organization Test[124]	1	44	-0.85 (-1.84, 0.14)	NE	ND
Immediate Recall[124]	1	44	**-0.63 (-1.03, -0.23)**	NE	olanzapine
IOWA gambling[71]	1	111	**-16.02 (-31.31, -0.73)**	NE	olanzapine
Level of Functioning Scale[58]	1	63	0.00 (-2.87, 2.87)	NE	ND
LNS[54,110,134]	3	120	0.56 (-1.99, 3.11)	63%	ND
memory: Z mean score[127]	1	309	-0.19 (-0.39, 0.01)	NE	ND
MMSE[105]	1	73	**-3.89 (-6.32, -1.46)**	NE	olanzapine
Motor function[105,124,127,145]	4	502	**-0.39 (-0.76, -0.02)**	74%	olanzapine
neurocognitive composite score[101,108,145]	3	595	-0.06 (-0.44, 0.32)	86%	ND
Nonverbal Fluency[124]	1	44	-3.40 (-6.52, -0.28)	NE	olanzapine
Nonverbal Fluency and Construction[124]	1	44	-0.66 (-1.36, 0.04)	NE	ND
Peabody Picture Vocabulary Test[124]	1	44	-2.68 (-9.54, 4.18)	NE	ND
Poor attention[105]	1	73	**-0.59 (-1.05, -0.13)**	NE	olanzapine
Processing speed and attention[145]	1	76	**-0.49 (-0.87, -0.11)**	NE	olanzapine
Rey auditory verbal learning (# words recalled)[71]	1	111	-3.09 (-7.35, 1.17)	NE	ND
Rey auditory verbal learning LTR (# words recalled from list after delay)[71]	1	111	**-1.40 (-2.69, -0.11)**	NE	olanzapine
Rey complex figure test (long term recall)[71]	1	111	0.10 (-2.60, 2.80)	NE	ND
Rey Auditory Verbal Learning Test, recognition form[75,110]	2	243	**-0.20 (-0.35, -0.06)**	0%	olanzapine
Rey Auditory Verbal Learning Test, sum of trials 1-5[110]	1	35	**-19.61 (-28.53, -10.69)**	NE	olanzapine
Rey-Taylor Complex Figure Copy[124]	1	44	-1.92 (-5.53, 1.69)	NE	ND
Rey-Taylor Complex Figure Immediate Recall[124]	1	44	-0.08 (-3.89, 3.73)	NE	ND
Similarities Subtest[124]	1	44	0.50 (-1.47, 2.47)	NE	ND
SRT[54,124]	2	69	-2.98 (-8.21, 2.24)	0%	ND
Stoop[54]	1	25	0.22 (-4.48, 4.92)	NE	ND
Trail Making Test A[75,105,110]	3	316	-0.38 (-1.17, 0.41)	79%	ND
Trail Making Test B[71,75,110,124]	4	398	8.79 (-6.26, 23.85)	66%	ND
Unweighted Neurocognitive Composite Score based on Z score (change score)[108]	1	263	**0.16 (0.04, 0.28)**	NE	haloperidol
VCCQ-intensity score[136]	1	31	-5.90 (-12.36, 0.56)	NE	ND
VCCQ-mood score[136]	1	31	8.20 (-1.79, 18.19)	NE	ND
VCCQ-sick[136]	1	31	**11.20 (0.85, 21.55)**	NE	haloperidol
Verbal STM[54]	1	25	-4.22 (-11.62, 3.18)	NE	ND

Table 88. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Verbal Memory[105]	1	73	**-0.82 (-1.26, -0.38)**	NE	Olanzapine
Verbal Fluency and Reasoning[124]	1	44	**-0.32 (-0.61, -0.03)**	NE	olanzapine
Verbal List Learning[124]	1	44	**-8.52 (-14.18, -2.86)**	NE	olanzapine
Visual Memory Span Backward[54]	1	25	0.11 (-1.64, 1.86)	NE	ND
Visual Memory Span Forward[54]	1	25	0.54 (-1.11, 2.19)	NE	ND
Visual Memory[105]	1	73	0.21 (-0.37, 0.79)	NE	ND
Visual Digit Coding Task[110]	1	35	**-10.57 (-17.24, -3.90)**	NE	olanzapine
Visual Reproduction[124]	1	44	-0.90 (-2.78, 0.98)	NE	ND
Visual Span[124]	1	44	-0.78 (-2.70, 1.14)	NE	ND
WAIS III backwards digits (total score)[71]	1	111	0.41 (-0.34, 1.16)	NE	ND
WAIS III digit symbol (total score)[71,75]	2	319	-0.29 (-0.83, 0.24)	28%	ND
WCST[134]	1	60	0.80 (-0.15, 1.75)	NE	ND
VCCQ-energy score[136]	1	31	**11.50 (3.69, 19.31)**	NE	haloperidol
WCS Test total errors[137]	1	29	**9.32 (2.63, 16.01)**	NE	haloperidol
WCST, perseverative errors[110,124]	2	79	0.05 (-0.07, 0.17)	0%	ND
Social relatedness/ functioning					
Subjective well-being, social functioning subscale[78]	1	24	-0.90 (-4.23, 2.43)	NE	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; COWA = Controlled Oral Word Association; COWAT = Controlled Oral Word Association Test; CRT = Clinical Global Impressions; CVLT = California Verbal Learning Test; DS CPT = Degraded Stimuli–Continuous Performance Test; DSC = Degraded Stimuli–Continuous; GCI = General Cognitive Index; GPT = Grooved Pegboard Test; I^2 = I–squared; LNS = Letter–Number Sequencing; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SRT = Simple Reaction Time; STM = short-term memory; VCCQ = Voris Cocaine Craving Questionnaire; WAIS = Wechsler Adult; Intelligence Scale; WCST = Wisconsin Card Sorting Test

Table 89. Evidence summary table: haloperidol versus quetiapine

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - elated mood subscale[79]	1	288	0.53 (-0.17, 1.23)	NE	ND
Negative symptoms					
PANSS - Depressive subscale[79]	1	288	**1.06 (0.32, 1.80)**	NE	quetiapine
Functional capacity					
Cognition - Attention Span[123]	1	25	-0.20 (-0.68, 0.28)	NE	ND
Cognition - Executive skills/visuomotor tracking[123]	1	25	0.10 (-0.42, 0.62)	NE	ND
Cognition - General[123]	1	25	-0.10 (-0.49, 0.29)	NE	ND
Cognition - Immediate recall[123]	1	25	-0.20 (-0.67, 0.27)	NE	ND
Cognition - Motor speed/dexterity[123]	1	25	0.10 (-1.04, 1.24)	NE	ND
Cognition - Verbal reasoning/fluency[123]	1	25	-0.20 (-0.58, 0.18)	NE	ND
Cognition - Visuospatial fluency/construction[123]	1	25	-0.60 (-1.29, 0.09)	NE	ND
Cognitive - composite score[75]	1	207	-0.14 (-0.33, 0.05)	NE	ND
Cognitive - Summary Score[143]	1	58	-0.11 (-0.61, 0.39)	NE	ND
Complex Figure Copy Test[123]	1	25	-1.30 (-3.09, 0.49)	NE	ND
Complex Figure Recall Test[123]	1	25	**1.00 (0.10, 1.90)**	NE	haloperidol
Design Learning Test[123]	1	25	-0.40 (-1.35, 0.55)	NE	ND
Finger Tapping[123]	1	25	-0.40 (-1.56, 0.76)	NE	ND
Grooved Pegboard[75,123]	2	232	-0.02 (-0.25, 0.21)	0%	ND
Hopkins Verbal Learning[143]	1	58	-1.52 (-5.84, 2.80)	NE	ND
Nonverbal fluency[123]	1	25	-0.10 (-0.46, 0.26)	NE	ND
Paragraph Recall[143]	1	58	-0.72 (-3.05, 1.60)	NE	ND
Rey Auditory Verbal Learning Test[75]	1	207	0.00 (-0.26, 0.26)	NE	ND
Story Recall Test[123]	1	25	-1.00 (-1.91, -0.09)	NE	
Stroop Color-Word[143]	1	58	-2.57 (-13.52, 8.37)	NE	ND
Symbol Digit[143]	1	58	1.14 (-7.55, 9.83)	NE	ND
Trail Making Test A[75]	1	207	-0.04 (-0.22, 0.14)	NE	ND
Trail Making Test B[75,123]	2	232	**-0.12 (-0.24, -0.01)**	0%	quetiapine
Trails B-A[143]	1	58	-1.00 (-33.10, 31.10)	NE	ND
Verbal Fluency[123,143]	2	83	-0.42 (-1.02, 0.17)	0%	ND
Verbal Learning Test[123]	1	25	0.00 (-0.91, 0.91)	NE	ND
Visual Organization Test[123]	1	25	0.00 (-0.48, 0.48)	NE	ND
WAIS-III Digit Symbol[75]	1	207	-0.26 (-0.46, -0.06)	NE	ND
WAIS-R Digit Symbol Test[123]	1	25	0.00 (-0.36, 0.36)	NE	ND
WAIS-R Similarities[123]	1	25	-0.30 (-0.77, 0.17)	NE	ND
WCST (perseverations)[123]	1	25	0.50 (-0.53, 1.53)	NE	ND
WMS Digit Span[123]	1	25	-0.10 (-0.53, 0.33)	NE	ND
WMS Visual Reproduction[123]	1	25	-0.10 (-1.44, 1.24)	NE	ND
WMS Visual Span[123]	1	25	-0.50 (-1.23, 0.23)	NE	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale

Table 90. Evidence summary table: haloperidol versus risperidone

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
BPRS - Hostility/suspiciousness subscale[113]	1	63	0.05 (-0.13, 0.23)	NE	ND
PANSS-derived BPRS - activity subscale[120]	1	1362	0.30 (-0.11, 0.71)	NE	ND
PANSS-derived BPRS - hostility subscale[120]	1	1362	0.08 (-0.38, 0.54)	NE	ND
PANSS - hostility subscale[62,72]	2	443	0.47 (-0.13, 1.06)	0%	ND
PANSS - excitement factor[145]	1	78	-0.15 (-0.73, 0.43)	NE	ND
PANSS - positive factor[145]	1	78	0.03 (-0.38, 0.44)	NE	ND
PANSS - Uncontrolled hostility/excitement MADRS[118]	1	289	**-0.70 (-1.18, -0.22)**	NE	haloperidol
SCL-90-R - Anger/hostility subscale[113]	1	63	**0.22 (0.04, 0.40)**	NE	risperidone
SCL-90-R - Obsessive/compulsive subscale[113]	1	63	**0.35 (0.13, 0.57)**	NE	risperidone
SCL-90-R - Paranoid ideation subscale[113]	1	63	0.16 (-0.16, 0.48)	NE	ND
SCL-90-R - Psychotiscism subscale[113]	1	63	0.17 (-0.09, 0.43)	NE	ND
Negative symptoms					
BPRS - emotional withdrawal subscale[113]	1	63	0.00 (-0.17, 0.17)	NE	ND
CDS-S - depression subscale[45]	1	20	2.30 (-0.42, 5.02)	NE	ND
PANSS - 5-factor solution[118]	1	289	-1.40 (-2.93, 0.13)	NE	ND
PANSS - negative factor[145]	1	78	-0.14 (-0.53, 0.25)	NE	ND
PANSS-derived BPRS - Anergia[120]	1	1362	0.36 (-0.12, 0.84)	NE	ND
SANS - Affective Flattening[113]	1	63	-0.02 (-0.35, 0.31)	NE	ND
SANS - Alogia[113]	1	63	-0.01 (-0.29, 0.27)	NE	ND
SANS - Anhedonia[113]	1	63	0.11 (-0.24, 0.46)	NE	ND
SANS - Attentional impairment score[118]	1	289	-0.20 (-0.47, 0.07)	NE	ND
SANS - Avolition[113]	1	63	0.06 (-0.26, 0.38)	NE	ND
SANS - Global[113]	1	63	0.04 (-0.21, 0.29)	NE	ND
SCL-90 - Depression subscale[113]	1	63	**0.46 (0.22, 0.70)**	NE	risperidone
General psychopathology					
BPRS - Factor I[60]	1	62	**-0.52 (-0.84, -0.20)**	NE	haloperidol
BPRS - anxiety/depression subscale[113,117]	2	98	0.18 (-0.13, 0.49)	51%	ND
BPRS - Factor II[60]	1	62	-0.17 (-0.46, 0.12)	NE	ND
BPRS - Factor III[60]	1	62	-0.11 (-0.51, 0.29)	NE	ND
BPRS - Factor IV[60]	1	62	-0.09 (-0.22, 0.04)	NE	ND
BPRS - Factor V[60]	1	62	-0.13 (-0.45, 0.19)	NE	ND
BPRS - Thought disturbances subscale[113,117]	2	98	-0.10 (-0.33, 0.12)	0%	ND
PANSS - anxiety/depression subscale[72,118,145]	3	732	0.25 (-0.26, 0.77)	50%	ND
PANSS - Cognitive subscale[145]	1	78	-0.13 (-0.42, 0.16)	NE	ND
PANSS - disorganized thought subscale[72,118]	2	654	-0.25 (-2.91, 2.41)	93%	ND
PANSS-derived BPRS - Anxiety/depression subscale[120]	1	1362	0.33 (-0.15, 0.81)	NE	ND
PANSS-derived BPRS - Thought disturbances subscale[120]	1	1362	-0.06 (-0.62, 0.50)	NE	ND

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Total score					
SCL–9–R - Anxiety subscale[113]	1	63	**0.35 (0.13, 0.57)**	NE	risperidone
SCL–90–R - Interpersonal sensitivity subsclae[113]	1	63	**0.33 (0.05, 0.61)**	NE	risperidone
SCL–90–R - Phobic Anxiety subscale[113]	1	63	**0.33 (0.09, 0.57)**	NE	risperidone
SCL–90–R - Somatization subscale[113]	1	63	0.21 (-0.01, 0.43)	NE	ND
Functional capacity					
Attention Span[124]	1	44	0.08 (-0.24, 0.40)	NE	ND
Brief test of attention (correct responses)[71]	1	117	-0.51 (-1.54, 0.52)	NE	ND
Continuous performance test (correct responses)[71]	1	117	-2.45 (-6.83, 1.93)	NE	ND
COWAT[71,124,132,134]	4	776	-0.95 (-4.20, 2.31)	62%	ND
CVLT[134]	1	60	6.20 (-0.31, 12.71)	NE	ND
Design List Learning[124]	1	44	-3.78 (-9.34, 1.78)	NE	ND
Digit Span[124]	1	44	0.20 (-1.42, 1.82)	NE	ND
Digit Symbol Subtest[124]	1	44	0.20 (-4.34, 4.74)	NE	ND
Discrimination of self-generated words[100]	1	9	-0.01 (-0.12, 0.10)	NE	ND
DS CPT[134]	1	60	-0.01 (-0.06, 0.04)	NE	ND
DSC[134]	1	60	0.40 (-6.41, 7.21)	NE	ND
Early night[45]	1	20	244.45 (-49.52, 538.42)	NE	ND
Executive Skills[124]	1	44	0.11 (-0.51, 0.73)	NE	ND
Fagerstrom Tolerance Questionnaire[102]	1	76	**1.90 (0.94, 2.86)**	NE	haloperidol
Finger Tapping[71,124]	2	161	0.44 (-6.66, 7.54)	65%	ND
GAF[118]	1	289	-2.20 (-5.64, 1.24)	NE	ND
GPT[134]	1	60	-1.40 (-25.41, 22.61)	NE	ND
Grooved Pegboard[71,124]	2	161	-0.48 (-17.58, 16.61)	64%	ND
Hooper Visual Organization Test[124]	1	44	0.38 (-0.47, 1.23)	NE	ND
Immediate Recall[124]	1	44	-0.22 (-0.58, 0.14)	NE	ND
IOWA gambling[71]	1	117	-11.99 (-26.45, 2.47)	NE	ND
Late night[45]	1	20	88.89 (-1.54, 179.32)	NE	ND
LNS[134]	1	60	0.20 (-2.40, 2.80)	NE	ND
Maze tasks CM velocity[107]	1	20	**-41.70 (-81.21, -2.19)**	NE	risperidone
Maze tasks SM velocity[107]	1	20	**-48.00 (-94.88, -1.12)**	NE	risperidone
Morning[45]	1	20	-200.00 (-561.65, 161.65)	NE	ND
Motor Skills[124]	1	44	-0.48 (-1.10, 0.14)	NE	ND
Neurocognitive composite score[101]	1	255	-0.06 (-0.27, 0.15)	NE	ND
Neurocognitive Global Score[145]	1	78	**-0.46 (-0.73, -0.19)**	NE	risperidone
Neurocognitive testing - Declarative verbal learning and memory[145]	1	78	**-0.66 (-1.08, -0.24)**	NE	risperidone
Neurocognitive testing - General executive and perceptual organization[145]	1	78	**-0.44 (-0.77, -0.11)**	NE	risperidone
Neurocognitive testing - Simple motor Functioning[145]	1	78	-0.24 (-0.72, 0.24)	NE	ND
Nonverbal Fluency[124]	1	44	**-3.60 (-6.17, -1.03)**	NE	risperidone
Nonverbal Fluency and Construction[124]	1	44	0.24 (-0.24, 0.72)	NE	ND
Peabody Picture Vocabulary Test[124]	1	44	1.02 (-4.41, 6.45)	NE	ND
Perception of emotion[99]	1	18	**-6.93 (-10.32, -3.54)**	NE	risperidone

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Neurocognitive testing - Processing speed and attention[145]	1	78	-0.21 (-0.63, 0.21)	NE	ND
Processing speed: WAIS-R Digit Symbol age-corrected score[132]	1	555	**-0.35 (-0.67, -0.03)**	NE	risperidone
Rey auditory verbal learning (# words recalled)[71]	1	117	-1.26 (-5.18, 2.66)	NE	ND
Rey auditory verbal learning LTR (# words recalled from list after delay)[71]	1	117	-0.98 (-2.36, 0.40)	NE	ND
Rey complex figure test (long term recall)[71]	1	117	-0.46 (-2.97, 2.05)	NE	ND
Rey Verbal Learning Test: trials 1-5[132]	1	555	-1.47 (-3.08, 0.14)	NE	ND
Rey-Taylor Complex Figure Copy[124]	1	44	2.31 (-0.36, 4.98)	NE	ND
Rey-Taylor Complex Figure Immediate Recall[124]	1	44	-0.08 (-4.15, 3.99)	NE	ND
RVLT: Long-delay free recall[132]	1	555	**-0.63 (-1.12, -0.14)**	NE	risperidone
RVLT: Recognition discriminability[132]	1	555	-0.78 (-2.85, 1.29)	NE	ND
Similarities Subtest[124]	1	44	-0.65 (-2.11, 0.81)	NE	ND
Sleep time (hrs)[45]	1	20	-0.46 (-2.22, 1.30)	NE	ND
SRM 5 s[146]	1	67	1.60 (-0.20, 3.40)	NE	ND
SRM 15 s[146]	1	67	1.50 (-0.20, 3.20)	NE	ND
Story Recall Test[124]	1	44	-2.45 (-7.44, 2.54)	NE	ND
SWM 5 s[146]	1	67	-1.50 (-4.69, 1.69)	NE	ND
SWM 15s[146]	1	67	-2.90 (-5.92, 0.12)	NE	ND
Trail Making Test B[71,124]	2	161	2.64 (-9.02, 14.30)	0%	ND
Verbal Fluency and Reasoning[124]	1	44	**-0.30 (-0.49, -0.11)**	NE	risperidone
Verbal List Learning[124]	1	44	-2.27 (-7.50, 2.96)	NE	ND
Vigilance: Continuous Performance Test d' total[132]	1	555	0.08 (-0.01, 0.17)	NE	ND
Visual Reproduction[124]	1	44	0.45 (-1.33, 2.23)	NE	ND
Visual Span[124]	1	44	0.47 (-1.31, 2.25)	NE	ND
Waking bouts[45]	1	20	7.26 (-1.46, 15.98)	NE	ND
WAIS III backwards digits (total score)[71]	1	117	-0.07 (-0.84, 0.70)	NE	ND
WAIS III digit symbol (total score)[71]	1	117	-0.30 (-1.42, 0.82)	NE	ND
WCST Categories[107,132,134]	3	635	-0.21 (-0.84, 0.41)	37%	ND
WCST Nonperseverative errors[107]	1	20	19.10 (-10.11, 48.31)	NE	ND
WCST Perseverative errors[107,124,132]	3	619	0.58 (-2.92, 4.08)	12%	ND
WCST Perseverative responses[107]	1	20	5.10 (-16.83, 27.03)	NE	ND
WMS_RVR: Delayed recall total[132]	1	555	-0.81 (-2.15, 0.53)	NE	ND
WMS_RVR: Immediate recall total score[132]	1	555	-0.05 (-1.07, 0.97)	NE	ND
Functional deterioration					
Deterioration (Csernasky criterion)[118]	1	289	**0.87 (0.46, 1.64)**	NE	haloperidol
Marked clinical deterioration[118]	1	289	**0.84 (0.29, 2.44)**	NE	haloperidol

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Social relatedness/ functioning					
Improvement[135]	1	100	**0.65 (0.45, 0.93)***	NE	risperidone
Social Adjustment Scale II-Instrumental role[113]	1	63	-0.01 (-0.55, 0.53)	NE	ND
Social Adjustment Scale II-Intimate relationship[113]	1	63	**0.47 (0.01, 0.93)**	NE	haloperidol
Social Adjustment Scale II-Overall Social functioning[113]	1	63	0.18 (-0.18, 0.54)	NE	ND
Social Adjustment Scale II-Sense of wellbeing[113]	1	63	0.12 (-0.20, 0.44)	NE	ND
Social Adjustment Scale II - Total Social relatedness/functioning[113]	1	63	0.05 (-0.25, 0.35)	NE	ND
Social Adjustment Scale II-Social/leisure[113]	1	63	-0.06 (-0.42, 0.30)	NE	ND
SOFAS[118]	1	289	-1.80 (-5.14, 1.54)	NE	ND
Total score[118]	1	289	-1.10 (-4.45, 2.25)	NE	ND
Facial Emotion Identification Test[134]	1	60	-0.50 (-2.26, 1.26)	NE	ND
Half profile nonverbal sensitivity[134]	1	60	**5.20 (0.45, 9.95)**	NE	haloperidol
Interpersonal Perception Task - 15[134]	1	60	0.30 (-0.62, 1.22)	NE	ND
Voice Emotion Identification Test[134]	1	60	0.50 (-1.51, 2.51)	NE	ND

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CARS–M = Clinician-Administered Rating Scale for Mania; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; CI = confidence intervals; CM = Complex Maze; COWAT = Controlled Word Association Test; CVLT = California Verbal Learning Test; DSC–CPT = Degraded Stimuli–Continuous Performance Test; GAF = Global Assessment of Functioning; GPT = Grooved Pegboard Test; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; I^2 = I–squared; LNS = Letter–Number Sequencing; LQLP = Lancashire Quality of Life Profile; MADRS = Montgomery-Asberg Depression Rating Scale; ND = no difference; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PPI = Prepulse Inhibition; QLS = Quality of Life Scale; QoL = quality of life; RVLT = Rey Verbal Learning Test; SADS–C = Schedule for Affective Disorders and Schizophrenia–Change; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check Lis; SM = simple maze; SOFAS = Social and Occupational Functioning Scale; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; WAIS–R = Wechsler Adult Intelligence Scale–Revised; WCST = Wisconsin Card Sort Test; WMS-RVR = Wechsler Memory Scale - Revised Visual Reproduction; YMRS = Young Mania Rating Scale

Table 91. Evidence summary table: haloperidol versus ziprasidone

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Functional capacity					
Cognitive composite score[75]	1	185	-0.08 (-0.28, 0.12)	NE	ND
Purdue Pegboard Test[75]	1	185	**0.30 (0.05, 0.55)**	NE	haloperidol
RVLT[75]	1	185	-0.24 (-0.48, 0.00)	NE	ND
Trail Making Test A[75]	1	185	-0.06 (-0.27, 0.15)	NE	ND
Trail Making Test B[75]	1	185	-0.19 (-0.39, 0.01)	NE	ND
WAIS-III Digit Symbol[75]	1	185	-0.19 (-0.41, 0.03)	NE	ND

Note: bold = statistically significant; * = binary outcome; I^2 = I–squared; ND = no difference; NE = not estimable; RVLT = Rey's Auditory Verbal Learning Test; WAIS = Wechsler Adult Intelligence Scale

B) Bipolar Disorder

Table 92. Evidence summary table: haloperidol versus aripiprazole

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
PANSS - Hostility subscale[33]	1	332	-0.50 (-1.09, 0.09)	NE	ND
Mood-Mania					
CGI-BP - Mania subscale[32,33]	2	679	0.13 (-0.17, 0.43)	44%	ND
Mood-Depression					
CGI-BP - Depression subscale[32,33]	2	679	0.01 (-0.16, 0.18)	0%	ND
General psychopathology					
PANSS - cognitive subscale[33]	1	332	-0.70 (-1.81, 0.41)	NE	ND

Note: bold = statistically significant; * = binary outcome; CGI—BP = Clinical Global Impressions—Bipolar; I^2 = I–squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 93. Evidence summary table: haloperidol versus risperidone

Outcome	Studies	Participants	Effect Estimate	I^2	Favors
Positive symptoms					
PANSS - hostility subscale[90]	1	62	0.70 (-1.35, 2.75)	NE	ND
Mood-Mania					
CARS-M - Mania subscale[90]	1	62	4.00 (-1.66, 9.66)	NE	ND
Mood-Depression					
HAM-D - core depression[90]	1	62	1.70 (-1.13, 4.53)	NE	ND
HAM-D - Secondary symptoms[90]	1	62	1.00 (-0.62, 2.62)	NE	ND
HAM-D - sleep disturbance[90]	1	62	1.80 (0.20, 3.40)	NE	olanzapine
HAM-D - Somatic symptoms[90]	1	62	0.70 (-0.44, 1.84)	NE	ND
General psychopathology					
PANSS - anxiety/depression subscale[90]	1	62	-0.30 (-2.64, 2.04)	NE	ND
PANSS - disorganized thought subscale[90]	1	62	0.10 (-2.31, 2.51)	NE	ND

Note: bold = statistically significant; * = binary outcome; CARS-M = Clinician-Administered Rating Scale for Mania; HAM-D = Hamilton Rating Scale for Depression; I2 = I–squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Appendix M. Subgroup and Sensitivity Analyses

Table 94. Subgroup and sensitivity analyses: chlorpromazine vs. clozapine – Total Score (BPRS)

Total Symptoms (BPRS)	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	6	535	**8.40 (5.92, 10.88)**	20%	clozapine
Race					
Asian	2	80	4.73 (-0.39,9.85)	0%	ND
Mixed	4	455	**9.57 (7.36,11.8)**	0%	clozapine
First time vs. other					
Previous episodes	4	474	**9.63 (7.40,11.86)**	0%	clozapine
Mixed first and previous episodes	2	61	4.77 (-0.17,9.71)	0%	ND
Treatment resistance					
Treatment resistant	2	308	**10.22 (7.12,13.33)**	10%	clozapine
Mixed	4	227	**6.96 (3.94,9.97)**	0%	clozapine
Duration of followup					
>6weeks	3	191	**6.70 (3.55, 9.84)**	0%	clozapine
≤6weeks	3	304	**10.32 (7.66, 12.98)**	0%	clozapine
Dosage of FGA (chlorpromazine)					
Up to 1800mg/d	4	474	**9.63 (7.40,11.9)**	0%	clozapine
Maximum 100 and 600mg/d	2	61	4.77 (-0.17,9.71)	0%	ND
Source of funding					
Industry funding	2	283	**11.1 (8.13,14.0)**	0%	clozapine
No industry funding reported	4	252	**6.72 (3.89, 9.54)**	0%	clozapine
Risk of bias					
Unclear	4	363	**8.23 (3.82, 12.6)**	45%	clozapine
High	2	172	**7.59 (4.20, 11.0)**	0%	clozapine
Imputations					
Data imputed	3	206	**6.77 (2.39, 11.15)**	20%	clozapine
No data imputed	3	329	**9.70 (7.03, 12.37)**	5%	clozapine

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference

Table 95. Subgroup and sensitivity analyses: haloperidol vs. aripiprazole – Response rates

Response Rates	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	6	2175	1.01 (0.76, 1.34)	83%	ND
Disorder subtypes					
Schizoaffective included	3	531	0.93 (0.41, 2.11)	87%	ND
Mixed or schizoaffective disorder excluded	2	1654	0.94 (0.75, 1.16)	74%	ND
Co-morbid drug/alcohol use					
Excluded	3	767	0.89 (0.57, 1.38)	64%	ND
Mixed	2	1418	1.13 (0.62, 2.06)	94%	ND
First time vs. other					
Mixed first and previous episodes	4	891	1.06 (0.72, 1.57)	79%	ND
Multiple episodes only	1	1294	**0.85 (0.75, 0.96)**	NE	aripiprazole
Treatment resistance					
Treatment resistant excluded	3	1778	1.10 (0.80, 1.51)	89%	ND
Mixed	2	108	0.35 (0.03, 3.93)	69%	ND
Duration of followup					
>6weeks	2	1393	0.37 (0.04, 3.76)	68%	ND
≤6weeks	3	792	1.12 (0.80, 1.57)	80%	ND
Dosage of FGA (haloperidol)					
<15mg/d	4	2061	0.90 (0.73, 1.11)	60%	ND
Up to 30mg/d	1	124	**1.55 (1.20, 2.00)**	NE	haloperidol
Dosage of SGA (aripiprazole)					
Up to 30mg/d	4	2061	0.90 (0.73, 1.11)	60%	ND
>30mg/d	1	124	**1.55 (1.20, 2.00)**	NE	haloperidol
Source of funding					
Industry funding	4	2061	0.90 (0.73, 1.11)	60%	ND
No industry funding reported	1	124	**1.55 (1.20, 2.00)**	NE	haloperidol
Risk of bias					
Unclear	3	1654	0.94 (0.75, 1.16)	74%	ND
High	2	531	0.93 (0.41, 2.11)	87%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; ND = no difference; NE = not estimable; mg = milligrams; SGA = second generation antipsychotic

Table 96. Subgroup and sensitivity analyses: haloperidol vs. olanzapine - Positive symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	14	3742	0.43 (-0.22,1.08)	36%	ND
Disorder subtypes					
Schizoaffective disorder	1	76	1.20 (-2.07, 4.47)	NE	ND
Mixed	13	3666	0.38 (-0.30, 1.07)	41%	ND
Co-morbid drug/alcohol use					
Excluded	4	527	-0.44 (-2.75, 1.87)	51%	ND
Included only	1	31	-2.00 (-4.82, 0.82)	NE	ND
Mixed	9	3184	**0.70 (0.15, 1.26)**	17%	olanzapine
Treatment resistance					
Treatment resistant	5	2207	0.26 (-1.26, 1.78)	53%	ND
No treatment resistance	1	44	2.18 (-0.59, 4.95)	NE	ND
Mixed	8	1491	0.32 (-0.51, 1.15)	30%	ND
Duration of followup					
≤6 weeks	2	58	-2.08 (-4.59, 0.43)	0%	ND
>6 weeks and <6 months	7	694	0.21 (-1.19, 1.62)	48%	ND
≥6 months	5	2990	**0.77 (0.30, 1.24)**	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	12	3593	**0.62 (0.03, 1.21)**	23%	olanzapine
Upper limit >20mg/d	2	149	-0.62 (-3.62, 2.38)	60%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	12	3593	**0.62 (0.03, 1.21)**	23%	olanzapine
>20mg/d	2	149	-0.62 (-3.62, 2.38)	60%	ND
Source of funding					
Industry funding	13	3560	0.33 (-0.38, 1.05)	40%	ND
No industry funding reported	1	182	1.15 (-0.55, 2.85)	NE	ND
Risk of bias					
Unclear	11	1688	0.45 (-0.36, 1.25)	36%	ND
High	3	2054	-0.12 (-2.21, 1.98)	51%	ND
Race					
Other	13	3466	0.34 (-0.36, 1.04)	39%	ND
Asian	1	276	1.30 (-0.65, 3.25)	NE	ND
Data analysis					
Imputed data	2	336	-0.66 (-2.68, 1.36)	68%	ND
No imputed data	12	3406	**0.74 (0.11, 1.37)**	17%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 97. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Negative symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	14	3742	**1.06 (0.46, 1.67)**	27%	olanzapine
Disorder subtypes					
Schizoaffective disorder specifically included	1	76	2.50 (-0.18, 5.18)	NE	ND
Mixed	13	3666	**0.99 (0.37, 1.62)**	29%	olanzapine
Co-morbid drug/alcohol use					
Excluded	4	527	0.88 (-0.63, 2.39)	0%	ND
Included only	1	31	**-3.20 (-6.03, -0.37)**	NE	haloperidol
Mixed	9	3184	**1.27 (0.82, 1.72)**	2%	olanzapine
Treatment resistance					
Treatment resistant	5	2207	**1.28 (0.11, 2.44)**	40%	olanzapine
Mixed	8	1491	0.90 (-0.02, 1.81)	35%	ND
No treatment resistance	1	44	1.02 (-2.39, 4.43)	NE	ND
Duration of followup					
≤6 weeks	2	58	-1.87 (-5.12, 1.39)	42%	ND
>6 weeks and <6 months	7	694	**1.37 (0.25, 2.50)**	25%	olanzapine
≥6 months	5	2990	**1.26 (0.79, 1.73)**	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	12	3593	**1.13 (0.51, 1.75)**	24%	olanzapine
Upper limit >20mg/d	2	149	0.92 (-1.78, 3.62)	65%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	12	3593	**1.13 (0.51, 1.75)**	24%	olanzapine
>20mg/d	2	149	0.92 (-1.78, 3.62)	65%	ND
Source of funding					
Industry funding	13	3560	**1.08 (0.40, 1.76)**	32%	olanzapine
No industry funding reported	1	182	0.82 (-0.69, 2.33)	NE	ND
Risk of bias					
Unclear	11	1688	**1.18 (0.58, 1.78)**	0%	olanzapine
High	3	2054	-0.33 (-3.82, 3.16)	79%	ND
Race					
Other	13	3466	**0.97 (0.34, 1.59)**	27%	olanzapine
Asian	1	276	**2.40 (0.35, 4.45)**	NE	olanzapine
Data analysis					
Imputed data	2	336	0.69 (-1.04, 2.41)	56%	ND
No imputed data	12	3406	**1.14 (0.45, 1.83)**	28%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 98. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – General psychopathology (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	10	1187	0.53 (-1.20, 2.25)	52%	ND
Disorder subtypes					
Schizoaffective disorder	1	76	3.20 (-0.95, 7.35)	NE	ND
Mixed	9	1111	0.24 (-1.60, 2.08)	54%	ND
Co-morbid drug/alcohol use					
Excluded	3	500	0.02 (-2.77, 2.81)	25%	ND
Included only	1	31	**-6.10 (-10.90, -1.30)**	NE	haloperidol
Mixed	6	656	1.50 (-0.12, 3.12)	25%	ND
Treatment resistance					
Treatment resistant	3	184	1.49 (-2.58, 5.56)	68%	ND
Mixed	6	959	0.05 (-2.23, 2.32)	60%	ND
No treatment resistance	1	44	1.35 (-4.82, 7.52)	NE	ND
Duration of followup					
≤6 weeks	1	31	**-6.10 (-10.90, -1.30)**	NE	haloperidol
>6 weeks and <6 months	6	418	0.79 (-1.48, 3.05)	47%	ND
≥6 months	3	738	**1.71 (0.08, 3.35)**	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	8	1038	0.60 (-1.35, 2.55)	51%	ND
Upper limit >20mg/d	2	149	0.40 (-4.73, 5.54)	74%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	8	1038	0.60 (-1.35, 2.55)	51%	ND
>20mg/d	2	149	0.40 (-4.73, 5.54)	74%	ND
Source of funding					
Industry funding	9	1005	0.32 (-1.64, 2.27)	56%	ND
No industry funding reported	1	182	1.93 (-1.17, 5.03)	NE	ND
Risk of bias					
Unclear	8	1129	1.08 (-0.43, 2.58)	33%	ND
High	2	58	-2.54 (-9.93, 4.85)	73%	ND
Data analysis					
Imputed data	8	851	0.65 (-1.56, 2.86)	52%	ND
No imputed data	2	336	0.10 (-3.67, 3.87)	75%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 99. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	**15**	**4209**	**2.31 (0.44, 4.18)**	**37%**	**olanzapine**
Disorder subtypes					
Paranoid schizophrenia	1	28	-0.65 (-4.77, 3.47)	NE	ND
Schizoaffective disorder	3	593	2.13 (-0.91, 5.17)	0%	ND
Mixed	11	3588	**2.65 (0.17, 5.12)**	42%	olanzapine
Co-morbid drug/alcohol use					
Excluded	3	483	-0.73 (-5.83, 4.38)	0%	ND
Mixed	12	3726	**2.71 (0.75, 4.67)**	40%	olanzapine
Treatment resistance					
Treatment resistant	6	2231	2.54 (-2.21, 7.29)	56%	ND
Mixed	8	1770	2.25 (0.00, 4.50)	23%	ND
No treatment resistance	1	208	0.90 (-3.81, 5.61)	NE	ND
Duration of followup					
≤6 weeks	2	51	-4.88 (-17.94, 8.18)	0%	ND
>6 weeks and <6 months	7	695	2.26 (-1.85, 6.37)	61%	ND
≥6 months	6	3463	**3.47 (1.99, 4.94)**	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	13	4060	**2.74 (1.02, 4.46)**	23%	olanzapine
>20mg/d	2	149	0.79 (-10.00, 11.58)	77%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	13	4060	**2.74 (1.02, 4.46)**	23%	olanzapine
Upper limit >20mg/d	2	149	0.79 (-10.00, 11.58)	77%	ND
Source of funding					
Industry funding	13	4003	**2.21 (0.15, 4.26)**	45%	olanzapine
No industry funding reported	2	206	3.34 (-2.21, 8.90)	0%	ND
Risk of bias					
Unclear	13	2005	2.01 (-0.30, 4.33)	35%	ND
High	2	2204	**3.30 (0.27, 6.34)**	41%	olanzapine
Race					
Other	14	3933	**2.01 (0.13, 3.89)**	36%	olanzapine
Asian	1	276	**7.90 (0.96, 14.84)**	NE	olanzapine
Data analysis					
Imputed data	3	364	-1.50 (-4.54, 1.54)	0%	ND
No imputed data	12	3845	**3.68 (2.17, 5.18)**	5%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 100. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (BPRS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	13	4014	0.59 (-1.10, 2.28)	82%	ND
Disorder subtypes					
Paranoid schizophrenia	1	28	8.85 (-3.92, 21.62)	NE	ND
Schizoaffective disorder	2	182	0.99 (-2.19, 4.17)	0%	ND
Mixed	10	3804	0.33 (-1.56, 2.22)	86%	ND
Co-morbid drug/alcohol use					
Excluded	6	1124	-2.37 (-6.19, 1.44)	90%	ND
Mixed	7	2890	**2.05 (0.55, 3.55)**	36%	olanzapine
Treatment resistance					
Treatment resistant	4	2205	-5.50 (-14.1, 3.07)	95%	ND
Mixed	9	1809	**1.10 (0.62, 1.58)**	0%	olanzapine
Duration of followup					
≤6 weeks	6	771	-2.00 (-5.42, 1.42)	90%	ND
>6 weeks and <6 months	4	549	**2.86 (0.50, 5.22)**	0%	olanzapine
≥6 months	3	2694	1.63 (-0.72, 3.97)	55%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	11	3832	0.49 (-1.38, 2.37)	85%	ND
>20mg/d	2	182	0.99 (-2.19, 4.17)	0%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	10	3800	0.55 (-1.41, 2.52)	86%	ND
Upper limit >20mg/d	3	214	0.57 (-2.16, 3.30)	0%	ND
Source of funding					
Industry funding	9	3570	-0.42 (-3.48, 2.64)	88%	ND
No industry funding reported	4	444	**1.12 (0.61, 1.63)**	0%	olanzapine
Risk of bias					
Unclear	9	1725	-0.84 (-4.35, 2.67)	86%	ND
High	4	2289	**1.78 (0.36, 3.21)**	66%	olanzapine
Race					
Other	12	3738	0.28 (-1.48, 2.04)	83%	ND
Asian	1	276	**4.40 (0.33, 8.47)**	NE	olanzapine

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 101. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (CGI–S Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	8	3564	0.14 (-0.05, 0.33)	89%	ND
Disorder subtypes					
Schizoaffective disorder	2	271	0.20 (-0.35, 0.75)	34%	ND
Mixed	6	3293	0.13 (-0.08, 0.34)	92%	ND
Co-morbid drug/alcohol use					
Excluded	5	1097	0.03 (-0.13, 0.20)	61%	ND
Mixed	3	2467	**0.28 (0.19, 0.38)**	0%	olanzapine
Treatment resistance					
Treatment resistant	2	2059	**0.24 (0.01, 0.47)**	32%	olanzapine
Mixed	5	1297	0.07 (-0.10, 0.24)	71%	ND
No treatment resistance	1	208	0.60 (-0.23, 1.43)	NE	ND
Duration of followup					
≤6 weeks	2	336	-0.06 (-0.19, 0.06)	47%	ND
>6 weeks and <6 months	1	63	0.00 (-0.47, 0.47)	NE	ND
≥6 months	5	3165	**0.26 (0.16, 0.37)**	7%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	7	3501	0.15 (-0.05, 0.36)	90%	ND
Upper limit >20mg/d	1	63	0.00 (-0.47, 0.47)	NE	ND
Dosage of SGA (olanzapine)					
≤20mg/d	7	3501	0.15 (-0.05, 0.36)	90%	ND
>20mg/d	1	63	0.00 (-0.47, 0.47)	NE	ND
Source of funding					
Industry funding	7	3453	**0.20 (0.07, 0.32)**	33%	olanzapine
No industry funding reported	1	111	**-0.10 (-0.14, -0.06)**	NE	haloperidol
Risk of bias					
Unclear	4	1186	0.13 (-0.01, 0.27)	11%	ND
High	4	2378	0.13 (-0.19, 0.45)	94%	ND
Data analysis					
Imputed data	1	263	0.17 (-0.08, 0.42)	NE	ND
No imputed data	7	3301	0.13 (-0.08, 0.35)	90%	ND

Significant results are in bold. CGI–S = Clinical Global Impression–Severity; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 102. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	14	4099	**0.86 (0.78, 0.96)**	55%	**olanzapine**
Disorder subtypes					
Schizoaffective disorder	2	327	0.73 (0.33, 1.63)	95%	ND
Mixed	12	3772	0.87 (0.80, 0.95)	26%	olanzapine
Co-morbid drug/alcohol use					
Only	1	24	1.33 (0.38, 4.72)	NE	ND
Excluded	2	378	1.02 (0.79, 1.32)	29%	ND
Mixed	11	3697	**0.84 (0.75, 0.94)**	61%	olanzapine
Treatment resistance					
Treatment resistant	5	2247	0.81 (0.62, 1.04)	70%	ND
Mixed	8	1644	**0.92 (0.85, 0.99)**	0%	olanzapine
No treatment resistance	1	208	**0.52 (0.37, 0.72)**	NE	olanzapine
Duration of followup					
≤6 weeks	4	519	0.96 (0.87, 1.07)	0%	ND
>6 weeks and <6 months	5	590	0.83 (0.68, 1.01)	22%	ND
≥6 months	5	2990	0.83 (0.68, 1.01)	74%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	12	3907	**0.86 (0.78, 0.96)**	48%	olanzapine
>20mg/d	2	192	0.79 (0.42, 1.47)	85%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	11	3875	**0.86 (0.77, 0.96)**	53%	olanzapine
Upper limit >20mg/d	3	224	0.80 (0.50, 1.29)	70%	ND
Source of funding					
Industry funding	9	3631	**0.83 (0.73, 0.95)**	66%	olanzapine
No industry funding reported	5	468	0.97 (0.85, 1.11)	0%	ND
Risk of bias					
Unclear	9	1641	**0.91 (0.83, 0.99)**	7%	olanzapine
High	5	2458	0.81 (0.64, 1.02)	78%	ND
Race					
Other	13	3823	**0.86 (0.76, 0.97)**	59%	olanzapine
Asian	1	276	0.87 (0.76, 1.00)	NE	ND
Data analysis					
Imputed data	3	360	0.80 (0.56, 1.13)	42%	ND
No imputed data	11	3739	**0.87 (0.78, 0.98)**	61%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 103. Subgroup and sensitivity analyses: haloperidol vs. quetiapine – Negative symptoms (PANSS)*

Negative Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	4	393	1.36 (-0.41, 3.13)	76%	ND
Disorder subtypes					
Schizoaffective disorder	1	45	-1.20 (-4.49, 2.09)	NE	ND
Mixed	3	348	**1.87 (0.09, 3.65)**	77%	quetiapine
Co-morbid drug/alcohol use					
Excluded	1	25	3.10 (-1.60, 7.80)	NE	ND
Mixed	3	368	1.12 (-0.86, 3.10)	83%	ND
Treatment resistance					
Treatment resistant	1	288	0.61 (-0.57, 1.79)	NE	ND
Mixed	3	105	1.65 (-0.93, 4.23)	61%	ND
Duration of followup					
≤6 months	2	323	1.70 (-0.34, 3.75)	88%	ND
>6 months	2	70	0.61 (-3.55, 4.77)	54%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	4	393	1.36 (-0.41, 3.13)	76%	ND
Upper limit >20mg/d	0	0	NE	NE	NE
Dosage of SGA (quetiapine)					
Lower range ≤250mg/d	1	45	-1.20 (-4.49, 2.09)	NE	ND
Lower range >250mg/d	3	348	**1.87 (0.09, 3.65)**	77%	quetiapine
Risk of bias					
Unclear	3	358	0.53 (-0.81, 1.87)	10%	ND
High	1	35	**2.70 (1.92, 3.48)**	NE	quetiapine

*All studies were industry-funded. Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 104. Subgroup and sensitivity analyses: haloperidol vs. quetiapine – response rates*

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	6	1421	0.99 (0.76, 1.30)	77%	**ND**
Disorder subtypes					
Schizoaffective disorder	1	45	0.64 (0.21, 1.96)	NE	ND
Mixed	5	1376	1.01 (0.77, 1.34)	81%	ND
Co-morbid drug/alcohol use					
Excluded	1	123	**1.62 (1.24, 2.11)**	NE	haloperidol
Mixed	5	1298	0.90 (0.73, 1.10)	47%	ND
Treatment resistance					
Treatment resistant	2	411	1.08 (0.49, 2.41)	95%	ND
Mixed	4	1010	1.00 (0.85, 1.17)	6%	ND
Duration of followup					
≤6 months	3	881	1.22 (0.93, 1.61)	71%	ND
>6 months	3	540	**0.74 (0.60, 0.91)**	0%	quetiapine
Dosage of FGA (haloperidol)					
≤20mg/d	5	1298	0.90 (0.73, 1.10)	47%	ND
Upper limit >20mg/d	1	123	**1.62 (1.24, 2.11)**	NE	haloperidol
Dosage of SGA (quetiapine)					
Lower range ≤250mg/d	5	1133	1.08 (0.82, 1.42)	69%	ND
Lower range >250mg/d	1	288	**0.73 (0.56, 0.94)**	NE	quetiapine
Risk of bias					
Unclear	3	663	0.85 (0.62, 1.15)	44%	ND
High	3	778	1.12 (0.76, 1.64)	83%	ND

*All studies were industry-funded. Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 105. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Positive symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	20	4043	0.64 (-0.06, 1.34)	53%	ND
Disorder subtypes					
Schizoaffective disorder	4	1181	0.64 (-0.55, 1.83)	47%	ND
Schizoaffective excluded	2	363	2.70 (-1.10, 6.50)	47%	ND
Mixed	14	2499	0.48 (-0.42, 1.38)	57%	ND
Co-morbid drug/alcohol use					
Excluded	14	3210	0.46 (-0.42, 1.34)	58%	ND
Mixed	6	833	**1.24 (0.44, 2.03)**	0%	risperidone
First vs. multiple episodes					
Mixed first and multiple episodes	12	1876	**1.04 (0.21, 1.86)**	30%	risperidone
Multiple episodes only	7	1984	0.10 (-1.17, 1.36)	70%	ND
First episode only	1	183	0.10 (-1.98, 2.18)	NE	ND
Treatment resistance					
No treatment resistant	4	881	0.32 (-1.44, 2.08)	80%	ND
Treatment resistant	2	156	-0.00 (-3.04, 3.03)	56%	ND
Mixed	14	3006	**0.84 (0.07, 1.60)**	36%	risperidone
Duration of followup					
≤6 weeks	3	260	1.07 (-1.51, 3.64)	41%	ND
>6 weeks and <6 months	10	2147	0.26 (-0.44, 0.96)	0%	ND
≥6 months	7	1636	0.91 (-0.39, 2.21)	81%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	17	3881	0.48 (-0.21, 1.17)	51%	ND
Upper limit >20mg/d	2	106	3.28 (-0.33, 6.89)	58%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	15	3754	0.68 (-0.08, 1.45)	59%	ND
Upper range >6mg/d	13	3394	-0.01 (-0.67, 0.64)	29%	ND
Source of funding					
Industry funding	10	2091	0.68 (-0.38, 1.74)	66%	ND
No industry funding	11	2317	**0.85 (0.02, 1.67)**	34%	risperidone
Risk of bias					
Unclear	15	3488	0.46 (-0.34, 1.26)	55%	ND
High	5	555	**1.52 (0.57, 2.47)**	0%	risperidone
Race					
Other	15	3813	0.74 (-0.06, 1.54)	63%	ND
Asian	5	230	0.18 (-1.32, 1.67)	0%	ND
Data analysis					
Imputed data	3	1439	0.01 (-0.89, 0.90)	0%	ND
No imputed data	17	2604	0.77 (-0.05, 1.60)	60%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 106. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Negative symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	20	4043	**0.60 (0.01, 1.20)**	30%	risperidone
Disorder subtypes					
Schizoaffective disorder	4	1181	**0.88 (0.12, 1.64)**	0%	risperidone
Schizoaffective excluded	2	363	**2.36 (0.39, 4.32)**	0%	risperidone
Mixed	14	2499	0.32 (-0.51, 1.16)	35%	ND
Co-morbid drug/alcohol use					
Excluded	14	3210	0.52 (-0.22, 1.26)	31%	ND
Mixed	6	833	0.77 (-0.37, 1.91)	37%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	13	2059	**0.88 (0.30, 1.47)**	0%	risperidone
Multiple episodes only	7	1984	0.05 (-1.19, 1.29)	57%	ND
Treatment resistance					
No treatment resistant	4	881	-0.04 (-1.78, 1.70)	73%	ND
Treatment resistant	2	156	1.00 (-1.74, 3.73)	41%	ND
Mixed	14	3006	**0.71 (0.15, 1.27)**	3%	risperidone
Duration of followup					
≤6 weeks	3	260	1.05 (-0.84, 2.95)	0%	ND
>6 weeks and <6 months	10	2147	0.54 (-0.21, 1.29)	0%	ND
≥6 months	7	1636	0.54 (-0.49, 1.57)	65%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	18	3937	0.56 (-0.03, 1.15)	28%	ND
Upper limit >20mg/d	2	106	1.82 (-2.85, 6.49)	71%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	15	3754	0.53 (-0.13, 1.19)	40%	ND
Upper range >6mg/d	10	3283	0.26 (-0.45, 0.96)	38%	ND
Source of funding					
Industry funding	10	2091	0.43 (-0.54, 1.41)	56%	ND
No industry funding not reported	10	1952	**0.76 (0.08, 1.45)**	0%	risperidone
Risk of bias					
Unclear	15	3488	0.39 (-0.30, 1.08)	35%	ND
High	5	555	**1.47 (0.44, 2.51)**	0%	risperidone
Race					
Other	15	3813	0.60 (-0.08, 1.28)	43%	ND
Asian	5	230	0.78 (-1.03, 2.59)	0%	ND
Data analysis					
Imputed data	3	1439	-0.40 (-2.38, 1.58)	18%	ND
No imputed data	17	2604	**0.74 (0.08, 1.41)**	32%	risperidone

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 107. Subgroup and sensitivity analyses: haloperidol vs. risperidone – General symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	16	3073	-2.54 (-6.39, 1.32)	96%	ND
Disorder subtypes					
Schizoaffective disorder	3	816	0.60 (-1.08, 2.27)	0%	ND
Schizoaffective excluded	1	41	8.90 (-0.51, 18.31)	NE	ND
Mixed	12	2216	-4.18 (-9.09, 0.72)	96%	ND
Co-morbid drug/alcohol use					
Excluded	12	2817	0.31 (-1.18, 1.80)	43%	ND
Mixed	4	256	-12.2 (-26.8, 2.51)	99%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	8	906	-4.07 (-14.33, 6.19)	97%	ND
Multiple episodes only	7	1984	-1.24 (-5.05, 2.57)	93%	ND
First episode only	1	41	8.90 (-0.51, 18.31)	NE	ND
Treatment resistance					
No treatment resistant	3	516	-1.13 (-3.95, 1.70)	42%	ND
Treatment resistant	2	156	1.51 (-1.22, 4.23)	0%	ND
Mixed	11	2401	-3.82 (-9.26, 1.61)	97%	ND
Duration of followup					
≤6 weeks	3	260	-11.31 (-44.1, 21.5)	99%	ND
>6 weeks and <6 months	9	1825	0.98 (-0.25, 2.20)	0%	ND
≥6 months	4	988	-2.76 (-7.19, 1.68)	94%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	13	2995	-2.79 (-6.84, 1.27)	96%	ND
Upper limit >20mg/d	1	78	1.10 (-2.78, 4.98)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	11	2784	-0.36 (-3.30, 2.58)	91%	ND
Upper range >6mg/d	9	2704	0.62 (-0.90, 2.14)	43%	ND
Source of funding					
Industry funding	6	1121	-0.16 (-2.05, 1.73)	37%	ND
No industry funding reported	10	1952	-4.41 (-10.45, 1.63)	97%	ND
Risk of bias					
Unclear	12	2840	0.52 (-0.75, 1.78)	28%	ND
High	4	233	-13.6 (-28.5, 1.41)	98%	ND
Race					
Other	11	2843	-3.44 (-8.34, 1.45)	97%	ND
Asian	5	230	0.01 (-2.83, 2.84)	33%	ND
Data analysis					
Imputed data	3	1439	0.99 (-0.60, 2.58)	0%	ND
No imputed data	13	1634	-3.07 (-7.73, 1.59)	96%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 108. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	20	4021	2.23 (-0.37, 4.83)	75%	ND
Disorder subtypes					
Schizoaffective disorder	4	1181	3.08 (-0.19, 6.34)	45%	ND
Schizoaffective excluded	2	363	**9.93 (0.77, 19.09)**	27%	risperidone
Mixed	14	2477	1.04 (-1.82, 3.90)	65%	ND
Co-morbid drug/alcohol use					
Excluded	14	3188	**2.56 (0.65, 4.47)**	18%	risperidone
Mixed	6	833	1.95 (-3.14, 7.04)	82%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	12	1854	**3.78 (1.37, 6.18)**	32%	risperidone
Multiple episodes only	7	1984	-0.56 (-3.98, 2.86)	65%	ND
First episode only	1	183	1.60 (-5.61, 8.81)	NE	ND
Treatment resistance					
No treatment resistant	3	837	3.53 (-0.06, 7.13)	46%	ND
Treatment resistant	2	156	2.52 (-3.99, 9.02)	0%	ND
Mixed	15	3028	1.89 (-1.10, 4.89)	71%	ND
Duration of followup					
≤6 weeks	4	280	5.89 (-0.00, 11.79)	30%	ND
>6 weeks and <6 months	10	2147	2.01 (-0.30, 4.32)	0%	ND
≥6 months	6	1594	1.06 (-3.29, 5.42)	90%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	19	3943	2.23 (-0.46, 4.93)	76%	ND
Upper limit >20mg/d	1	78	2.30 (-5.85, 10.45)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	14	3702	1.83 (-1.14, 4.79)	79%	ND
Upper range >6mg/d	12	3646	**2.95 (1.19, 4.70)**	20%	risperidone
Source of funding					
Industry funding	9	2049	**3.11 (1.23, 5.00)**	13%	risperidone
No industry funding reported	11	1972	1.67 (-2.15, 5.49)	71%	ND
Risk of bias					
Unclear	13	3416	**2.72 (1.17, 4.27)**	5%	risperidone
High	7	605	1.91 (-3.47, 7.29)	77%	ND
Race					
Other	15	3791	2.56 (-0.37, 5.48)	81%	ND
Asian	5	230	0.76 (-4.40, 5.92)	6%	ND
Data analysis					
Imputed data	3	1439	1.11 (-1.91, 4.13)	0%	ND
No imputed data	17	2582	2.66 (-0.31, 5.63)	79%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 109. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (BPRS)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	13	2592	0.51 (-0.17, 1.20)	44%	ND
Disorder subtypes					
Schizoaffective disorder	2	209	1.05 (-1.78, 3.87)	0%	ND
Schizoaffective excluded	2	363	**4.88 (0.88, 8.89)**	0%	risperidone
Mixed	9	1920	0.34 (-0.29, 0.98)	46%	ND
Co-morbid drug/alcohol use					
Excluded	7	1875	**0.84 (0.36, 1.32)**	0%	risperidone
Mixed	6	717	0.23 (-1.44, 1.90)	29%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	7	805	0.98 (-1.14, 3.10)	41%	ND
Multiple episodes only	5	1604	0.00 (-0.11, 0.11)	0%	ND
First episode only	1	183	1.10 (-3.07, 5.27)	NE	ND
Treatment resistance					
No treatment resistant	1	183	1.10 (-3.07, 5.27)	NE	ND
Treatment resistant	2	193	1.17 (-2.35, 4.68)	0%	ND
Mixed	10	2216	0.49 (-0.28, 1.27)	57%	ND
Duration of followup					
≤6 weeks	5	491	**0.82 (0.32, 1.32)**	0%	risperidone
>6 weeks and <6 months	6	1961	0.80 (-1.63, 3.23)	33%	ND
≥6 months	1	63	0.00 (-0.11, 0.11)	NE	ND
Dosage of FGA (haloperidol)					
≤20mg/d	11	2389	0.52 (-0.23, 1.27)	53%	ND
Upper limit >20mg/d	2	203	0.91 (-2.57, 4.38)	0%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	10	2421	**0.80 (0.33, 1.28)**	0%	risperidone
Upper range >6mg/d	9	2310	1.01 (-0.74, 2.75)	22%	ND
Source of funding					
Industry funding	6	666	0.00 (-0.11, 0.11)	0%	ND
No industry funding reported	7	1926	0.71 (-0.29, 1.71)	18%	ND
Risk of bias					
Unclear	10	2027	0.01 (-0.19, 0.21)	0%	ND
High	3	565	**0.95 (0.04, 1.85)**	7%	risperidone
Race					
Other	12	2557	0.53 (-0.18, 1.24)	49%	ND
Asian	1	35	-0.70 (-12.6, 11.2)	NE	ND
Data analysis					
Imputed data	5	1565	0.93 (-0.74, 2.60)	0%	ND
No imputed data	8	1027	0.49 (-0.36, 1.35)	65%	ND

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 110. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (CGI–S)

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	**8**	**2346**	0.03 (-0.17, 0.23)	**63%**	**ND**
Disorder subtypes					
Schizoaffective excluded	2	363	0.52 (-0.41, 1.46)	75%	ND
Mixed	6	1983	-0.10 (-0.24, 0.05)	30%	ND
Co-morbid drug/alcohol use					
Excluded	6	1957	0.01 (-0.23, 0.24)	66%	ND
Mixed	2	389	0.13 (-0.18, 0.45)	0%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	4	593	0.13 (-0.25, 0.50)	78%	ND
Multiple episodes only	4	1753	0.01 (-0.19, 0.21)	0%	ND
Treatment resistance					
No treatment resistant	1	289	-0.10 (-0.40, 0.20)	NE	ND
Treatment resistant	1	67	0.20 (-0.72, 1.12)	NE	ND
Mixed	6	1990	0.07 (-0.19, 0.34)	72%	ND
Duration of followup					
≤6 weeks	2	158	0.37 (-0.89, 1.64)	88%	ND
>6 weeks and <6 months	5	1899	0.11 (-0.08, 0.30)	0%	ND
≥6 months	1	289	-0.10 (-0.40, 0.20)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	6	2238	-0.05 (-0.22, 0.11)	50%	ND
Upper range >6mg/d	5	2127	0.11 (-0.11, 0.34)	39%	ND
Source of funding					
Industry funding	4	791	0.03 (-0.17, 0.23)	0%	ND
No industry funding reported	4	1555	0.07 (-0.31, 0.45)	76%	ND
Risk of bias					
Unclear	6	1907	0.10 (-0.14, 0.35)	28%	ND
High	2	439	-0.08 (-0.39, 0.23)	73%	ND
Race					
Other	7	2311	0.04 (-0.17, 0.26)	68%	ND
Asian	1	35	-0.30 (-1.58, 0.98)	NE	ND
Data analysis					
Imputed data	3	1464	0.09 (-0.17, 0.35)	0%	ND
No imputed data	5	882	0.03 (-0.23, 0.29)	71%	ND

Significant results are in bold. CGI–S = Clinical Global Impression–Severity; d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 111. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	16	3453	0.94 (0.87, 1.02)	29%	ND
Disorder subtypes					
Schizoaffective included	3	864	1.03 (0.95, 1.12)	0%	ND
Schizoaffective excluded	2	363	0.78 (0.56, 1.07)	42%	ND
Mixed	11	2226	0.93 (0.83, 1.03)	16%	ND
Co-morbid drug/alcohol use					
Excluded	10	1586	0.97 (0.91, 1.05)	0%	ND
Mixed	6	913	0.86 (0.68, 1.10)	66%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	8	1553	0.93 (0.81, 1.07)	48%	ND
Multiple episodes only	7	1717	0.95 (0.84, 1.07)	14%	ND
First episodes only	1	183	0.89 (0.70, 1.14)	NE	ND
Treatment resistance					
No treatment resistant	1	183	0.89 (0.70, 1.14)	NE	ND
Treatment resistant	3	271	0.82 (0.52, 1.29)	75%	ND
Mixed	12	2999	0.96 (0.88, 1.04)	18%	ND
Duration of followup					
≤6 weeks	6	524	0.97 (0.85, 1.11)	16%	ND
>6 weeks and <6 months	7	2019	0.86 (0.72, 1.03)	33%	ND
≥6 months	3	910	0.98 (0.85, 1.13)	48%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	15	3327	0.93 (0.85, 1.01)	26%	ND
Upper limit >20mg/d	1	126	1.09 (0.91, 1.29)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	13	3267	0.97 (0.90, 1.05)	21%	ND
Upper range >6mg/d	11	3056	0.94 (0.86, 1.03)	31%	ND
Source of funding					
Industry funding	8	1411	0.79 (0.63, 1.00)	53%	ND
No industry funding	8	2042	0.98 (0.91, 1.06)	0%	ND
Risk of bias					
Unclear	12	2788	0.93 (0.84, 1.01)	20%	ND
High	4	665	0.99 (0.82, 1.19)	56%	ND
Race					
Other	14	3340	0.96 (0.88, 1.04)	25%	ND
Asian	2	113	0.90 (0.55, 1.46)	65%	ND
Data analysis					
Imputed data	5	1530	0.92 (0.71, 1.18)	23%	ND
No imputed data	11	1923	0.94 (0.85, 1.03)	38%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 112. Subgroup and sensitivity analyses: haloperidol vs. ziprasidone – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I^2	Favors
OVERALL POOLED RESULTS	6	1283	0.98 (0.74,1.30)	80%	ND
Co-morbid drug/alcohol use					
Excluded	3	677	1.03 (0.92, 1.15)	0%	ND
Mixed	3	606	0.90 (0.49, 1.62)	91%	ND
Treatment resistance					
Treatment resistant	1	120	**1.54 (1.19, 2.00)**	NE	ziprasidone
No treatment resistance	3	1053	0.79 (0.56, 1.13)	84%	ND
Mixed	2	110	1.21 (0.74, 1.98)	0%	ND
Mixed and treatment resistant	3	230	**1.46 (1.16, 1.84)**	0%	ziprasidone
Duration of followup					
≤6 weeks	4	797	1.22 (0.91, 1.62)	66%	ND
>6 months	2	486	**0.68 (0.54, 0.85)**	0%	haloperidol
Dosage of FGA (haloperidol)					
≤20mg/d	5	1163	0.87 (0.66, 1.15)	70%	ND
Upper limit >20mg/d	1	120	**1.54 (1.19, 2.00)**	NE	ziprasidone
Dosage of SGA (ziprasidone)					
Lower limit <120mg/d	6	1283	0.98 (0.74,1.30)	80%	ND
Upper range >160mg/d	1	120	**1.54 (1.19, 2.00)**	NE	ziprasidone
Risk of bias					
Unclear	1	120	**1.54 (1.19, 2.00)**	NE	ziprasidone
High	5	1163	0.87 (0.66, 1.15)	70%	ND
Source of funding					
Industry-funded	4	1073	0.82 (0.59, 1.12)	76%	ND
Funding not reported	2	210	**1.50 (1.19, 1.91)**	0%	ziprasidone
Imputed Data					
Data imputed	3	958	0.93 (0.66, 1.31)	77%	ND
Data not imputed	3	325	1.02 (0.53, 1.97)	86%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I^2 = I–squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Appendix N. Summary Tables of Adverse Events

Chlorpromazine Versus Clozapine

Table 113. Evidence summary table: chlorpromazine versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Mortality[109,156]	2	214	0.98 (0.10, 9.19)	0%	ND
Withdrawals due to AE[63,87,109,152,160]	5	463	1.70 (0.65, 4.45)	34%	ND

AE = adverse event; I^2 = I–squared; ND = no difference

Table 114. Evidence summary table: chlorpromazine versus clozapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[153]	1	41	6.68 (0.37, 121.71)	NE	ND
Depression[152]	1	64	9.56 (0.54, 170.62)	NE	ND
Paranoia (increasing)[154]	1	15	0.30 (0.01, 6.29)	NE	ND
BMI and weight					
Weight gain (>5%)[87]	1	40	2.21 (0.79, 6.18)	NE	ND
Weight loss[87]	1	40	2.21 (0.22, 22.47)	NE	ND
Cardiovascular					
Abnormal ECG[154,160]	2	59	0.81 (0.39, 1.68)	0%	ND
Cardiotoxics effects[153]	1	41	NE	NE	ND
Hypertension[94,160]	2	312	**0.39 (0.17, 0.90)**	0%	chlorpromazine
Hypotension[48,87,94,109,160]	5	543	1.94 (0.91, 4.13)	49%	ND
Orthostatic hypotension[153,158,160]	3	110	0.61 (0.12, 3.09)	0%	ND
Tachycardia[87,94]	2	308	0.66 (0.37, 1.20)	0%	ND
Cholinergic and anticholinergic					
Dry mouth[63,87,94,152,161]	5	563	**3.00 (1.67, 5.40)**	11%	clozapine
Hypersalivation[48,63,87,94,152,154,158,160,161]	9	674	**0.25 (0.14, 0.45)**	13%	chlorpromazine
Ileus[109]	1	164	2.93 (0.12, 70.85)	NE	ND
CNS					
Dizziness[94,160,161]	3	352	0.62 (0.21, 1.87)	50%	ND
Drowsiness[94,152,153,160,161]	5	457	**0.75 (0.58, 0.97)**	0%	chlorpromazine
Sedation[48,63,87]	3	218	1.07 (0.69, 1.64)	0%	ND
Seizure[63,87,153]	3	232	2.91 (0.31, 27.28)	0%	ND
Slurred speech[160]	1	44	1.76 (0.08, 40.80)	NE	ND
Dermatology					
Dermatitis[109]	1	164	2.93 (0.12, 70.85)	NE	ND
Dermatologic problem[87]	1	40	5.50 (0.28, 107.78)	NE	ND
Exanthema or eczema[153]	1	41	8.59 (0.49, 150.00)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia[63]	1	151	4.94 (0.24, 101.10)	NE	ND
EPS					
Akathisia[63,87,154]	3	206	0.99 (0.37, 2.67)	0%	ND
Dystonia[63,154]	2	166	3.64 (0.43, 31.19)	0%	ND
EPS[48,63,87,109,158,160]	6	451	**2.75 (1.48, 5.12)**	0%	clozapine
Oculogyric crisis[154]	1	15	2.67 (0.13, 56.63)	NE	ND
Parkinsonism[153,154]	2	56	2.67 (0.13, 56.63)	NE	ND
Rigidity[63,152,160]	3	259	0.76 (0.10, 6.07)	58%	ND
Staggering[160]	1	44	0.57 (0.04, 8.53)	NE	ND
Tardive dyskinesia (deterioration)[87]	1	40	3.30 (0.14, 76.46)	NE	ND

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Tremor[152,160,161]	3	148	0.74 (0.28, 1.94)	7%	ND

Table 114. Evidence summary table: chlorpromazine versus clozapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Genito-urinary					
Impotence[63]	1	151	2.96 (0.12, 71.55)	NE	ND
GI					
Abdominal cramps[160]	1	44	1.76 (0.08, 40.80)	NE	ND
Constipation[63,94,109,152]	4	647	0.69 (0.44, 1.09)	0%	ND
Diarrhea[160]	1	44	0.38 (0.07, 2.04)	NE	ND
Heartburn[160]	1	44	1.76 (0.08, 40.80)	NE	ND
Nausea/vomiting[87,94,160]	3	352	1.06 (0.55, 2.04)	0%	ND
Hematology					
Agranulocytosis[63,94]	2	419	NE	NE	ND
Blood cell count (abnormal)[154]	1	15	NE	NE	ND
Neutropenia[109]	1	164	2.93 (0.12, 70.85)	NE	ND
Platelet count (elevated)[154]	1	15	0.07 (0.00, 1.03)	NE	ND
Leukocytopenia[48,63,87,94]	4	486	0.71 (0.18, 2.76)	55%	ND
Hepato-biliary					
Hepatic enzymes (elevated)[87,94]	2	308	0.79 (0.11, 5.71)	33%	ND
Jaundice[87]	1	40	3.30 (0.14, 76.46)	NE	ND
Sleep					
Deep sleep[153]	1	41	0.32 (0.01, 7.38)	NE	ND
Sleep disturbances[153]	1	41	6.68 (0.37, 121.71)	NE	ND
Respiratory and airway					
Cough[160]	1	44	0.20 (0.01, 4.53)	NE	ND
Systemic AE					
Fall (accident)[87]	1	40	0.22 (0.01, 4.31)	NE	ND
Fever/Chills[94,160]	2	312	**0.35 (0.15, 0.83)**	0%	chlorpromazine
Headache[94,160]	2	312	0.86 (0.43, 1.71)	0%	ND
Hyperthermia[109,154,160]	3	223	0.23 (0.05, 1.20)	0%	ND
Tension[160]	1	44	2.93 (0.15, 57.52)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Olanzapine

Table 115. Evidence summary table: chlorpromazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Withdrawals due to adverse events[66]	1	84	6.00 (0.75, 47.71)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 116. Evidence summary table: chlorpromazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Cardiovascular					
Orthostatic hypotension[66]	1	84	**7.50 (2.90, 19.42)**	NE	olanzapine
Tachycardia[66]	1	84	7.00 (0.90, 54.44)	NE	ND
Cholinergic and anticholinergic					
Dry mouth[66]	1	84	**1.94 (1.27, 2.97)**	NE	olanzapine
CNS					
Dizziness[66]	1	84	1.17 (0.43, 3.18)	NE	ND
Drowsiness/lethargy[66]	1	84	1.47 (0.89, 2.41)	NE	ND
Slurred speech[66]	1	84	9.00 (0.50, 162.10)	NE	ND
Unsteady gait[66]	1	84	**15.00 (2.07, 108.48)**	NE	olanzapine
EPS					
EPS[66]	1	84	1.75 (0.99, 3.08)	NE	ND
GI					
Constipation[66]	1	84	**2.60 (1.02, 6.65)**	NE	olanzapine
Dyspepsia/heartburn[66]	1	84	2.25 (0.75, 6.74)	NE	ND
Nausea/vomiting[66]	1	84	1.00 (0.31, 3.20)	NE	ND
Gentio-urinary					
Dysuria[66]	1	84	9.00 (0.50, 162.10)	NE	ND
Ophthalmology					
Blurred vision[66]	1	84	1.25 (0.36, 4.33)	NE	ND
Sleep					
Insomnia[66]	1	84	0.33 (0.07, 1.56)	NE	ND
Systemic AE					
Headache[66]	1	84	0.67 (0.30, 1.46)	NE	ND

Note: Bold = statistically significant; AE = adverse event; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Quetiapine

Table 117. Evidence summary table: chlorpromazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Severe AEs[121]	1	201	1.31 (0.92, 1.86)	NE	ND
Withdrawals due to AEs[121]	1	201	2.27 (0.72, 7.14)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 118. Evidence summary table: chlorpromazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[121]	1	201	2.02 (0.79, 5.17)	NE	ND
Anxiety[121]	1	201	1.35 (0.48, 3.74)	NE	ND
Nervousness[121]	1	201	2.53 (0.50, 12.71)	NE	ND
BMI and weight					
Weight gain[121]	1	201	0.67 (0.40, 1.14)	NE	ND
Cardiovascular					
Hypotension[121]	1	201	2.36 (0.63, 8.86)	NE	ND
Orthostatic hypotension[121]	1	201	**3.64 (1.40, 9.42)**	NE	quetiapine
Tachycardia[121]	1	201	1.01 (0.34, 3.03)	NE	ND
Cholinergic and anticholinergic					
Dry mouth[121]	1	201	0.76 (0.27, 2.10)	NE	ND
CNS					
Dizziness[121]	1	201	2.53 (0.50, 12.71)	NE	ND
Somnolence[121]	1	201	1.15 (0.60, 2.24)	NE	ND
EPS					
Akathasia[121]	1	201	1.52 (0.44, 5.21)	NE	ND
Hypertonia[121]	1	201	0.51 (0.13, 1.96)	NE	ND
Tremor[121]	1	201	0.51 (0.13, 1.96)	NE	ND
GI					
Constipation[121]	1	201	4.04 (0.88, 18.56)	NE	ND
Hepato-biliary					
Elevated ALT[121]	1	201	1.01 (0.30, 3.38)	NE	ND
Sleep					
Insomnia[121]	1	201	1.62 (0.77, 3.39)	NE	ND
Systemic AE					
Headache[121]	1	201	1.62 (0.55, 4.77)	NE	ND

Significant results are in bold; AE = adverse event; ALT = alanine transaminase; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Ziprasidone

Table 119. Evidence summary table: chlorpromazine versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Mortality[96]	1	306	NE	NE	ND
Withdrawals due to AEs[96]	1	306	1.32 (0.47, 3.70)	NE	ND

AE = adverse events; I^2 = I–squared; ND = no difference; NE = not estimable

Table 120. Evidence summary table: chlorpromazine versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
BMI and weight					
Weight gain[96]	1	306	3.29 (0.92, 11.72)	NE	ND
Weight loss[96]	1	306	**0.19 (0.06, 0.62)**	NE	chlorpromazine
Cardiovascular					
ECG abnormalities[96]	1	306	NE	NE	ND
Orthostatic hypotension[96]	1	306	2.63 (0.71, 9.73)	NE	ND
CNS					
Dizziness[96]	1	306	2.08 (0.97, 4.46)	NE	ND
Somnolence[96]	1	306	1.50 (0.99, 2.26)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea[96]	1	306	3.95 (0.45, 34.92)	NE	ND
EPS					
Akathisia[96]	1	306	1.43 (0.63, 3.24)	NE	ND
EPS[96]	1	306	1.09 (0.79, 1.49)	NE	ND
Tardive dyskinesia[96]	1	306	1.21 (0.61, 2.44)	NE	ND
Tremor[96]	1	306	0.42 (0.17, 1.07)	NE	ND
Genital, urinary, and breast					
Male sexual dysfunction[96]	1	306	0.42 (0.11, 1.61)	NE	ND
GI					
Vomiting[96]	1	306	0.74 (0.26, 2.08)	NE	ND

Significant results are in bold; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Fluphenazine Versus Olanzapine

Table 121. Evidence summary table: fluphenazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[89]	1	60	9.00 (0.51, 160.17)	NE	ND
Withdrawals due to AEs[89]	1	60	0.74 (0.51, 1.07)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 122. Evidence summary table: fluphenazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
BMI and weight					
Weight gain[89]	1	60	0.09 (0.01, 1.57)	NE	ND
CNS					
Stupor[89]	1	60	3.00 (0.13, 70.83)	NE	ND
EPS					
Akathisia[89]	1	60	0.33 (0.10, 1.11)	NE	ND
Dyskinesia[89]	1	60	0.25 (0.03, 2.11)	NE	ND
Dyskinetic symptoms[89]	1	60	2.00 (0.19, 20.90)	NE	ND
Hypertonia[89]	1	60	0.33 (0.04, 3.03)	NE	ND
Parkinsonism[89]	1	60	1.20 (0.41, 3.51)	NE	ND
Tremor[89]	1	60	1.50 (0.27, 8.34)	NE	ND
Sleep					
Insomnia[89]	1	60	0.08 (0.00, 1.31)	NE	ND

AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; I^2 = I–squared; ND = no difference; NE = not estimable

Fluphenazine Versus Quetiapine

Table 123. Evidence summary table: fluphenazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Withdrawals due to adverse events[67]	1	25	0.19 (0.01, 3.52)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 124. Evidence summary table: fluphenazine versus quetiapine – persistence and reversibility of adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Amenorrhea resolved by end of study[67]	1	25	NE	NE	ND
Gynecomastia resolved by end of study[67]	1	25	2.79 (0.12, 62.48)	NE	ND

I^2 = I–squared; ND = no difference; NE = not estimable

Table 125. Evidence summary table: fluphenazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Anxiety[67]	1	25	0.92 (0.06, 13.18)	NE	ND
Cardiovascular					
ECG abnormalities[67]	1	25	0.31 (0.01, 6.94)	NE	ND
Orthostatic hypotension[67]	1	25	1.85 (0.19, 17.84)	NE	ND
Cholinergic and anticholinergic					
Dry mouth[67]	1	25	0.46 (0.10, 2.08)	NE	ND
CNS					
Dizziness[67]	1	25	0.92 (0.06, 13.18)	NE	ND
Lethargy[67]	1	25	1.38 (0.28, 6.91)	NE	ND
Somnolence[67]	1	25	1.23 (0.34, 4.40)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea[67]	1	25	NE	NE	ND
Galactorrhea[67]	1	25	NE	NE	ND
EPS					
Tremor[67]	1	25	0.31 (0.01, 6.94)	NE	ND
Genital, urinary, and breast					
Gynecomastia[67]	1	25	2.79 (0.12, 62.48)	NE	ND
Urinary hesitancy[67]	1	25	0.92 (0.15, 5.56)	NE	ND
Urinary frequency[67]	1	25	0.31 (0.01, 6.94)	NE	ND
GI					
Constipation[67]	1	25	0.92 (0.29, 2.89)	NE	ND
Diarrhea[67]	1	25	0.19 (0.01, 3.52)	NE	ND
Dyspepsia/heartburn[67]	1	25	2.77 (0.33, 23.14)	NE	ND
Increased appetite[67]	1	25	0.62 (0.12, 3.07)	NE	ND
Nausea/vomiting[67]	1	25	1.85 (0.19, 17.84)	NE	ND
Ophthalmology					
Blurry vision[67]	1	25	0.92 (0.15, 5.56)	NE	ND
Sleep					
Insomnia[67]	1	25	1.54 (0.46, 5.09)	NE	ND
Systemic AE					
Headache[67]	1	25	0.92 (0.35, 2.41)	NE	ND

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Fluphenazine Versus Risperidone

Table 126. Evidence summary table: fluphenazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Withdrawals due to adverse events[67]	1	26	NE	NE	ND

I^2 = I–squared; ND = no difference; NE = not estimable

Table 127. Evidence summary table: fluphenazine versus risperidone – persistence and reversibility of adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Amenorrhea resolved by end of study[67]	1	26	0.33 (0.01, 7.50)	NE	ND
Gynecomastia resolved by end of study[67]	1	26	1.00 (0.07, 14.34)	NE	ND

I^2 = I–squared; ND = no difference; NE = not estimable

Table 128. Evidence summary table: fluphenazine versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Anxiety[67]	1	26	0.50 (0.05, 4.86)	NE	ND
Cardiovascular					
ECG abnormalities[67]	1	26	NE	NE	ND
Orthostatic hypotension[67]	1	26	0.40 (0.09, 1.70)	NE	ND
Cholinergic and anticholinergic					
Dry mouth[67]	1	26	1.00 (0.16, 6.07)	NE	ND
CNS					
Dizziness[67]	1	26	0.33 (0.04, 2.80)	NE	ND
Lethargy[67]	1	26	0.75 (0.21, 2.71)	NE	ND
Somnolence[67]	1	26	0.80 (0.28, 2.32)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea[67]	1	26	0.20 (0.01, 3.80)	NE	ND
Galactorrhea[67]	1	26	0.33 (0.01, 7.50)	NE	ND
EPS					
Tremor[67]	1	26	NE	NE	ND
Genital, urinary, and breast					
Gynecomastia[67]	1	26	1.00 (0.07, 14.34)	NE	ND
Urinary hesitancy[67]	1	26	5.00 (0.26, 95.02)	NE	ND
Urinary frequency[67]	1	26	0.33 (0.01, 7.50)	NE	ND
GI					
Constipation[67]	1	26	9.00 (0.53, 151.94)	NE	ND
Diarrhea[67]	1	26	0.20 (0.01, 3.80)	NE	ND
Dyspepsia[67]	1	26	3.00 (0.36, 25.21)	NE	ND
Increased appetite[67]	1	26	0.67 (0.13, 3.35)	NE	ND
Nausea[67]	1	26	0.67 (0.13, 3.35)	NE	ND
Ophthalmology					
Blurry vision[67]	1	26	1.00 (0.16, 6.07)	NE	ND
Sleep					
Insomnia[67]	1	26	1.67 (0.50, 5.57)	NE	ND
Systemic AE					
Headache[67]	1	26	0.71 (0.30, 1.67)	NE	ND

AE = adverse event; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Aripiprazole

Table 129. Evidence summary table: haloperidol versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[31,73,98]	3	1713	**1.11 (1.06, 1.17)**	0%	aripiprazole
Mortality[31,44]	2	655	0.77 (0.04, 15.91)	NE	ND
Serious AEs[31-33,44,76,92]	6	1741	0.84 (0.35, 2.03)	58%	ND
Withdrawals due to AEs[31-33,44,76,92,98]	7	3035	**1.25 (1.06, 1.47)**	0%	aripiprazole

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 130. Evidence summary table: haloperidol versus aripiprazole – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[31,44,74,98]	4	2253	1.09 (0.80, 1.48)	0%	ND
Anxiety[33,74,92,98]	4	2238	0.93 (0.73, 1.19)	0%	ND
Depression[32,33]	2	679	0.85 (0.26, 2.76)	82%	ND
Deterioration[73]	1	124	0.34 (0.01, 8.29)	NE	ND
Mania[33]	1	332	**0.20 (0.05, 0.91)**	NE	haloperidol
Psychosis[98]	1	1294	0.89 (0.69, 1.15)	NE	ND
BMI and weight					
Weight gain[33,92,98]	3	1934	1.03 (0.54, 1.96)	53%	ND
Cardiovascular					
ECG abnormalities[31,32,92]	3	950	1.33 (0.42, 4.19)	36%	ND
Orthostatic hypotension[92]	1	308	0.22 (0.03, 1.70)	NE	ND
Tachycardia[31]	1	295	1.57 (0.51, 4.82)	NE	ND
CNS					
Dizziness[31,44,92]	3	963	**0.53 (0.31, 0.90)**	0%	haloperidol
Seizure[31]	1	295	1.29 (0.05, 31.27)	NE	ND
Somnolence[31,33,44,74,92,98]	6	2893	**1.39 (1.03, 1.87)**	0%	aripiprazole
Dermatology					
Injection site reaction[31,44]	2	655	0.36 (0.09, 1.45)	0%	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia[32,33]	2	679	**3.67 (2.16, 6.24)**	70%	aripiprazole
EPS					
Akathisia[31-33,74,76,92,98]	7	2979	**2.04 (1.70, 2.44)**	0%	aripiprazole
Asthenia[92]	1	308	1.09 (0.37, 3.17)	NE	ND
Dystonia[31]	1	295	**7.83 (1.47, 41.76)**	NE	aripiprazole
EPS[32,33,44,74,92,98]	6	2945	**2.22 (1.37, 3.59)**	83%	aripiprazole
Hypertonia[92]	1	308	0.59 (0.17, 2.09)	NE	ND
Rigidity[33]	1	332	**8.10 (1.89, 34.66)**	NE	aripiprazole
Tremor[32,33,76,92,98]	5	2380	**1.99 (1.42, 2.78)**	4%	aripiprazole
GI					
Abdominal pain[92]	1	308	0.78 (0.31, 1.96)	NE	ND
Diarrhea[74]	1	304	1.01 (0.26, 3.98)	NE	ND
Dyspepsia[74]	1	304	**9.12 (1.17, 71.10)**	NE	aripiprazole
Nausea/Vomiting[31,44,74,92]	4	1267	**0.49 (0.28, 0.85)**	0%	haloperidol
Hepato-biliary					
Liver Damage[32]	1	347	3.05 (0.13, 74.41)	NE	ND
Ophthalmology					
Blurred vision[92]	1	308	**5.23 (1.42, 19.30)**	NE	aripiprazole
Sleep					
Insomnia[32,33,44,74,76,92,98]	7	3044	0.85 (0.59, 1.23)	65%	ND
Systemic AE					
Headache[31-33,44,74,92,98]	7	3240	1.00 (0.81, 1.24)	0%	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Asenapine

Table 131. Evidence summary table: haloperidol versus asenapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with adverse events[97]	1	335	1.09 (0.96, 1.25)	NE	ND
Serious adverse events[97]	1	335	0.96 (0.42, 2.17)	NE	ND
Withdrawals due to adverse events[97]	1	335	1.53 (0.74, 3.16)	NE	ND

I^2 = I–squared; ND = no difference; NE = not estimable

Table 132. Evidence summary table: haloperidol versus asenapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[97]	1	335	1.01 (0.47, 2.20)	NE	ND
Anxiety[97]	1	335	1.12 (0.45, 2.76)	NE	ND
Worse psychotic symptoms[97]	1	335	1.28 (0.54, 3.03)	NE	ND
BMI and weight					
Weight gain[97]	1	335	0.96 (0.33, 2.73)	NE	ND
Weight loss[97]	1	335	0.27 (0.01, 5.22)	NE	ND
CNS					
Oral hypoesthesia[97]	1	335	**0.04 (0.00, 0.69)**	NE	haloperidol
Sedation[97]	1	335	0.59 (0.20, 1.76)	NE	ND
Somnolence[97]	1	335	**0.21 (0.05, 0.90)**	NE	haloperidol
Endocrine (prolactin - thyroid)					
Abnormal Fasting glucose[97]	1	335	1.91 (0.39, 9.33)	NE	ND
Hyperprolactinemia[97]	1	335	**2.30 (1.02, 5.15)**	NE	asenapine
EPS					
Akathisia[97]	1	335	1.71 (0.93, 3.16)	NE	ND
Dystonia[97]	1	335	**3.51 (1.33, 9.24)**	NE	asenapine
EPS[97]	1	335	**2.07 (1.40, 3.07)**	NE	asenapine
Parkinsonism[97]	1	335	1.91 (0.99, 3.68)	NE	ND
Rigidity[97]	1	335	2.19 (0.81, 5.88)	NE	ND
GI					
Nausea/Vomiting[97]	1	335	0.48 (0.10, 2.22)	NE	ND
Sleep					
Insomnia[97]	1	335	0.75 (0.44, 1.27)	NE	ND
Systemic AE					
Headache[97]	1	335	0.64 (0.24, 1.71)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Clozapine

Table 133. Evidence summary table: haloperidol versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with adverse events[126]	1	423	0.81 (0.49, 1.34)	NE	ND
Mortality (Cohort)[163]	1	49625	**1.98 (1.30, 3.00)**	NE	clozapine
Withdrawals due to adverse events[55,95,105,126,145]	5	719	1.00 (0.66, 1.50)	0%	ND

Significant results are in bold; AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 134. Evidence summary table: haloperidol versus clozapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Clinical deterioration conducive to termination[145]	1	77	3.24 (0.70, 15.08)	NE	ND
Irritability[155]	1	88	**3.21 (1.26, 8.15)**	NE	clozapine
Overt aggression[145]	1	77	**1.66 (1.03, 2.66)**	NE	clozapine
BMI and weight					
Weight gain[105,145]	2	150	0.34 (0.01, 7.76)	80%	ND
Cardiovascular					
Hypertension[55]	1	75	2.57 (0.53, 12.42)	NE	ND
Hypertensive episodes[145]	1	77	0.22 (0.01, 4.35)	NE	ND
Intrathoracic oppression[155]	1	88	0.29 (0.06, 1.27)	NE	ND
Orthostatic hypotension[155]	1	88	0.48 (0.18, 1.24)	NE	ND
Palpitation[155]	1	88	0.29 (0.06, 1.27)	NE	ND
Cholinergic and anticholinergic					
Dry mouth[55,155]	2	163	**2.81 (1.61, 4.92)**	0%	clozapine
Hypersalivation[55]	1	75	**0.23 (0.12, 0.46)**	NE	haloperidol
CNS					
Dizziness[55,155]	2	163	0.84 (0.18, 3.95)	90%	ND
Drowsiness[155]	1	88	0.72 (0.40, 1.30)	NE	ND
Dysarthria[155]	1	88	1.72 (0.30, 9.79)	NE	ND
Sedation[55]	1	75	0.67 (0.39, 1.14)	NE	ND
Seizures[145]	1	77	0.12 (0.01, 2.15)	NE	ND
Seizures conducive to termination[145]	1	77	0.22 (0.01, 4.35)	NE	ND
Dermatology					
Pruritus[155]	1	88	0.23 (0.01, 4.63)	NE	ND
Rash[155]	1	88	0.23 (0.01, 4.63)	NE	ND
Endocrine (prolactin - thyroid)					
Abnormal menstruation[155]	1	88	3.44 (0.37, 31.79)	NE	ND
EPS					
Hyperkinesia[155]	1	88	**2.01 (1.13, 3.56)**	NE	clozapine
Hypertonia[155]	1	88	1.59 (0.89, 2.83)	NE	ND
Tardive Dyskinesia (Cohort)[162]	1	333	**34.50 (2.07, 573.55)**	NE	clozapine
Genital, urinary, and breast					
Enuresis[55]	1	75	0.15 (0.01, 2.74)	NE	ND
GI					
Constipation[55,155]	2	163	1.10 (0.62, 1.95)	0%	ND
Diarrhea[55,155]	2	163	0.75 (0.22, 2.55)	0%	ND
Loss of Appetite[155]	1	88	1.02 (0.43, 2.40)	NE	ND
Nausea/Vomiting[55,155]	2	163	**0.44 (0.21, 0.93)**	17%	haloperidol
Other GI[155]	1	88	0.46 (0.09, 2.24)	NE	ND
Hematology					
Agranulocytosis[126,145]	2	500	0.21 (0.02, 1.85)	0%	ND
Bruising[55]	1	75	NE	NE	ND
Hematological problems conducive to termination[145]	1	77	0.15 (0.01, 2.89)	NE	ND
Leukopenia[126]	1	423	0.47 (0.09, 2.54)	NE	ND
Neutropenia[126,145]	2	500	0.97 (0.41, 2.30)	0%	ND
Metabolic					
Abnormal Glucose levels[105]	1	73	**0.05 (0.00, 0.80)**	NE	haloperidol
Hypercholesterolemia[105]	1	73	0.08 (0.00, 1.35)	NE	ND
Hypertriglyceridemia[105]	1	73	0.39 (0.11, 1.34)	NE	ND
Metabolic syndrome (emergent)[105]	1	73	**0.27 (0.10, 0.75)**	NE	haloperidol
Ophthalmology					
Ophthalmic disturbances[155]	1	88	3.44 (0.37, 31.79)	NE	ND

Table 134. Evidence summary table: haloperidol versus clozapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Respiratory and airway					
Cough[155]	1	88	0.57 (0.11, 2.97)	NE	ND
Nasal congestion[155]	1	88	0.23 (0.03, 1.88)	NE	ND
Sore throat[55]	1	75	1.37 (0.33, 5.70)	NE	ND
Sleep					
Insomnia[155]	1	88	**3.44 (1.51, 7.84)**	NE	clozapine
Systemic AE					
Headache[155]	1	88	0.53 (0.24, 1.18)	NE	ND
Fever[55,155]	2	163	0.65 (0.36, 1.15)	0%	ND
Intercurrent illnesses conducive to termination[145]	1	77	0.36 (0.04, 3.31)	NE	ND
Malaise[55]	1	75	0.51 (0.23, 1.13)	NE	ND
Sweating[155]	1	88	0.13 (0.02, 0.96)	NE	ND
Weakness[155]	1	88	0.51 (0.17, 1.53)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Olanzapine

Table 135. Evidence summary table: haloperidol versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with adverse events[73]	1	119	10.47 (0.59, 185.18)	NE	ND
Persistence and reversibility of AE[88]	1	182	3.48 (0.99, 12.24)	NE	ND
Serious AEs[91,104,147]	3	741	1.41 (0.32, 6.21)	54%	ND
Withdrawals due to adverse events[43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159]	21	5351	**1.87 (1.55, 2.27)**	0%	olanzapine

Significant results are in bold; AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Abnormal thinking[101]	1	256	0.98 (0.37, 2.62)	NE	ND
Accommodation disturbance[159]	1	27	8.18 (0.43, 155.12)	NE	ND
Agitation[49,101]	2	523	1.25 (0.85, 1.85)	0%	ND
Anorexia[88]	1	182	**3.66 (1.25, 10.69)**	NE	olanzapine
Anxiety[49,88,101,147]	4	962	1.27 (0.90, 1.79)	0%	ND
Appetite (decreased)[141]	1	1996	**1.56 (1.25, 1.96)**	NE	olanzapine
Appetite (excessive)[141]	1	1996	**0.51 (0.41, 0.64)**	NE	haloperidol
Behavioral deterioration[73,84]	2	129	0.76 (0.05, 11.55)	39%	ND
Conversion symptoms[141]	1	1996	**2.34 (1.12, 4.88)**	NE	olanzapine
Depression[101]	1	256	0.64 (0.34, 1.23)	NE	ND
Excitement[88]	1	182	1.04 (0.54, 2.01)	NE	ND
Hallucinations[84,101]	2	266	1.06 (0.53, 2.11)	0%	ND
Nervousness[49,101]	2	523	1.45 (1.00, 2.11)	0%	ND
Overt aggression/violent behavior[49,110,145]	3	378	1.22 (0.54, 2.73)	52%	ND
Paranoia[101]	1	256	1.64 (0.71, 3.79)	NE	ND
Personality disorder[49]	1	267	0.51 (0.15, 1.68)	NE	ND
Suicidal ideation[110]	1	35	0.84 (0.06, 12.42)	NE	ND
Suicide[88]	1	182	3.13 (0.13, 75.92)	NE	ND
suicide (attempt)[88]	1	182	3.13 (0.13, 75.92)	NE	ND
BMI and weight					
Overweight/Obese[91,129]	2	274	**0.35 (0.21, 0.58)**	0%	haloperidol
Weight gain[49,71,88,91,101,104,105,108,127,129,140-142,145,159]	15	4600	**0.47 (0.37, 0.61)**	75%	haloperidol
Weight loss[88,141]	2	2178	2.43 (0.74, 7.99)	46%	ND
Cardiovascular					
ECG abnormalities[56,91]	2	433	0.34 (0.04, 3.21)	NE	ND
Hypertensive episodes[145]	1	76	NE	NE	ND
Hypotension[56]	1	225	0.30 (0.02, 5.19)	NE	ND
Palpitations[141]	1	1996	**1.48 (1.09, 2.02)**	NE	olanzapine
Cholinergic and anticholinergic					
Dry mouth[49,71,101,141,159]	5	2657	**0.75 (0.62, 0.91)**	0%	haloperidol
Hypersalivation[50,71,88,140,141,159]	6	3200	**3.38 (1.79, 6.38)**	49%	olanzapine
CNS					
Asthenia[49,71,159]	3	405	1.43 (1.00, 2.05)	0%	ND
Concentration difficulty[71]	1	111	3.93 (0.87, 17.68)	NE	ND
Dizziness[49,101,140]	3	976	0.69 (0.22, 2.20)	76%	ND
Drowsiness[141]	1	1996	**1.19 (1.02, 1.38)**	NE	olanzapine
Seizures[145]	1	76	NE	NE	ND
Somnolence[49,71,88,101,140,159]	6	1296	0.84 (0.63, 1.12)	35%	ND
Gait abnormalities[88]	1	182	**8.36 (1.98, 35.32)**	NE	olanzapine
Heaviness in extremities[141]	1	1996	**1.40 (1.11, 1.77)**	NE	olanzapine
Hypokinesia[71,140,141,159]	4	2587	**3.01 (1.88, 4.82)**	7%	olanzapine
Hypotonia[141]	1	1996	**1.68 (1.03, 2.72)**	NE	olanzapine
Dermatology					
Maculopapular rash[147]	1	257	0.35 (0.01, 8.43)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea[71]	1	111	4.91 (0.24, 100.05)	NE	ND
Hot flashes[141]	1	1996	**1.62 (1.06, 2.49)**	NE	olanzapine
Hyperprolactinemia[50,91,108]	3	902	NR	97%	ND

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
EPS					
Akathisia[49-51,56,71,88,91,101,104,108,127,140,141,159]	14	5031	**3.11 (2.43, 3.98)**	38%	olanzapine
Ataxia[141]	1	1996	**1.84 (1.01, 3.35)**	NE	olanzapine
Bradykinesia[88]	1	182	**8.36 (1.98, 35.32)**	NE	olanzapine
Dyskinesia[50,91,140,141]	4	3088	**3.55 (2.01, 6.27)**	10%	olanzapine
Dystonia[49,50,56,91,104,140,147,159]	8	2144	**5.01 (2.70, 9.28)**	0%	olanzapine
EPS[50,104,106,140,141,147]	6	3445	**3.88 (2.19, 6.85)**	69%	olanzapine
Hypertonia[49,50,140,141]	4	3147	**2.54 (1.65, 3.91)**	55%	olanzapine
Neuroleptic malignant syndrome[147]	1	257	3.12 (0.13, 75.83)	NE	ND
Parkinsonism[51,56,71,84,88,91,108,147]	8	1283	**4.28 (2.49, 7.35)**	50%	olanzapine
Rigidity[71,159]	2	138	**10.65 (2.08, 54.50)**	0%	olanzapine
Tardive dyskinesia[140]	1	453	11.75 (0.65, 211.26)	NE	ND
Tremor[49,50,71,88,101,104,140,141,159]	9	3999	**2.30 (1.59, 3.34)**	58%	olanzapine
Genital, urinary, and breast					
Difficult micturition[141]	1	1996	**1.68 (1.11, 2.54)**	NE	olanzapine
Ejaculatory dysfunction[71]	1	111	4.91 (0.24, 100.05)	NE	ND
Erectile dysfunction[71]	1	111	4.91 (0.59, 40.69)	NE	ND
Micturition disturbances[159]	1	27	3.40 (0.35, 32.90)	NE	ND
GI					
Constipation[49,101,159]	3	550	1.06 (0.43, 2.63)	23%	ND
Diarrhea[101]	1	256	1.64 (0.84, 3.20)	NE	ND
Dyspepsia[49]	1	267	1.32 (0.68, 2.54)	NE	ND
Nausea/Vomiting[49,88,101,141,141]	5	4697	**1.43 (1.06, 1.92)**	34%	olanzapine
Hematology					
Agranulocytosis[141,145]	2	2072	NE	NE	ND
Eosinophilia[50]	1	431	0.19 (0.01, 3.13)	NE	ND
Hematological problems conducive to termination[145]	1	76	NE	NE	ND
Neutropenia[145]	1	76	3.16 (0.13, 75.16)	NE	ND
Hepato-biliary					
Elevated ALT[50]	1	431	0.14 (0.02, 1.04)	NE	ND
Increased gGT[50]	1	431	0.33 (0.02, 5.79)	NE	ND
SGOT abnormality[108]	1	263	**0.41 (0.28, 0.58)**	NE	haloperidol
SGPT abnormality[49,108]	2	530	**0.46 (0.35, 0.62)**	0%	haloperidol
Metabolic					
Diabetes[129]	1	66	0.85 (0.21, 3.49)	NE	ND
Hypercholesterolemia[91,105]	2	281	**0.43 (0.26, 0.72)**	0%	haloperidol
Hyperglycemia[91,105]	2	281	**0.28 (0.12, 0.66)**	0%	haloperidol
Hypertriglyceridemia[91,105]	2	281	**0.53 (0.30, 0.92)**	0%	haloperidol
HDL (low)[91]	1	208	**0.38 (0.16, 0.94)**	NE	haloperidol
Metabolic syndrome[105,129]	2	139	0.38 (0.06, 2.51)	63%	ND
Ophthalmology					
Blurred vision[141]	1	1996	**1.40 (1.10, 1.78)**	NE	olanzapine
Respiratory and airway					
Rhinitis[49,101]	2	523	1.44 (0.90, 2.33)	0%	ND
Sleep					
Early awakening[141]	1	1996	**1.49 (1.24, 1.79)**	NE	olanzapine
Increased dreams/nightmares[141]	1	1996	**1.31 (1.05, 1.63)**	NE	olanzapine
Insomnia[49,50,88,101,104,127,141]	7	3717	**1.36 (1.03, 1.80)**	49%	olanzapine

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Systemic AE					
Chills[141]	1	1996	**1.74 (1.19, 2.52)**	NE	olanzapine
Fever[140]	1	453	**0.05 (0.00, 0.86)**	NE	haloperidol
Headache[49,50,101]	3	954	1.19 (0.85, 1.65)	0%	ND
Infection[140]	1	453	**0.27 (0.08, 0.93)**	NE	haloperidol
Increased perspiration[141]	1	1996	**1.91 (1.44, 2.54)**	NE	olanzapine
Injury[49]	1	267	0.86 (0.24, 3.04)	NE	ND
Intercurrent illnesses conducive to termination[145]	1	76	1.05 (0.07, 16.24)	NE	ND
Malaise[88]	1	182	0.94 (0.40, 2.21)	NE	ND
Pain[49,101]	2	523	0.81 (0.44, 1.50)	22%	ND
Tension[159]	1	27	14.73 (0.87, 248.02)	NE	ND

Significant results are in bold; AE = adverse event; ALT = alanine transaminase; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; gGT = serum gamma-glutamyl transferase; GI = gastrointestinal; HDL = high density lipoprotein; I^2 = I–squared; ND = no difference; NE = not estimable; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Haloperidol Versus Quetiapine

Table 137. Evidence summary table: haloperidol versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[68,73,79]	3	859	1.08 (0.93, 1.25)	25%	ND
Serious AEs[91]	1	207	1.68 (0.41, 6.86)	NE	ND
Withdrawals due to AEs[46,47,68,79,80,91,115,123]	8	1559	1.98 (0.79, 4.96)	73%	ND

AE = adverse event; I^2 = I–squared; ND = no difference NE = not estimable

Table 138. Evidence summary table: haloperidol versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[46,68,115,123]	4	984	0.83 (0.51, 1.36)	0%	ND
Anxiety[68]	1	448	1.86 (0.92, 3.76)	NE	ND
Asthenia[68]	1	448	**0.29 (0.12, 0.71)**	NE	haloperidol
Depression[115]	1	201	2.75 (0.75, 10.06)	NE	ND
Deterioration[73]	1	123	NE	NE	ND
Fatigue[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Irritability[123]	1	25	3.23 (0.14, 72.46)	NE	ND
BMI and weight					
Overweight[91]	1	207	0.65 (0.37, 1.14)	NE	ND
Weight gain[46,91,123]	3	542	**0.59 (0.39, 0.89)**	0%	haloperidol
Cardiovascular					
ECG abnormalities[46,91]	2	517	0.50 (0.05, 5.48)	NE	ND
Orthostatic hypotension[46,68,115]	3	959	**0.49 (0.25, 0.94)**	0%	haloperidol
Cholinergic and anticholinergic					
Dry mouth[68,115,123]	3	674	**0.32 (0.15, 0.65)**	0%	haloperidol
Hypersalivation[68,123]	2	473	1.88 (0.22, 16.18)	50%	ND
CNS					
Dizziness[46,68]	2	758	0.68 (0.36, 1.28)	0%	ND
Drowsiness[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Sedation[123]	1	25	3.23 (0.14, 72.46)	NE	ND
Somnolence[46,68,115,123]	4	984	**0.57 (0.39, 0.84)**	0%	haloperidol
Dermatology					
Dry skin/rash[123]	1	25	3.23 (0.14, 72.46)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea/Menstrual cycle irregularities[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Cold flashes[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Galactorrhea[47]	1	35	5.28 (0.27, 102.58)	NE	ND
Hyperprolactinemia[68,79,91]	3	943	**2.24 (1.04, 4.80)**	89%	quetiapine
Thyroid function test abnormalities[68]	1	448	**0.05 (0.00, 0.79)**	NE	haloperidol
EPS					
Akathisia[46,68,79,91,115]	5	1454	**3.51 (1.84, 6.72)**	68%	quetiapine
Akinesia[68]	1	448	2.92 (0.12, 71.32)	NE	ND
Cogwheel rigidity[68]	1	448	2.92 (0.12, 71.32)	NE	ND
Dyskinesia[91]	1	207	5.05 (0.25, 103.88)	NE	ND
Dystonia[46,68,91]	3	965	3.94 (0.79, 19.70)	29%	ND
EPS[46,68,79,80,115]	5	1292	NR	90%	ND
Fine tremors[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Hypertonia[68,79]	2	736	2.05 (0.82, 5.10)	60%	ND
Involuntary movement (jaw)[123]	1	25	0.36 (0.02, 8.05)	NE	ND
Neck rigidity[68]	1	448	2.92 (0.12, 71.32)	NE	ND
Oculogyric crisis[68]	1	448	6.82 (0.35, 131.19)	NE	ND
Parkinsonism[46,91]	2	517	**4.04 (1.97, 8.26)**	53%	quetiapine
Stiffness[123]	1	25	3.23 (0.14, 72.46)	NE	ND
Tardive dyskinesia[65]	1	35	NE	NE	ND
Tremor[68,115]	2	649	**3.80 (2.12, 6.81)**	0%	quetiapine
Twitch in the extremities[123]	1	25	0.36 (0.02, 8.05)	NE	ND
GI					
Constipation[46,68]	2	758	**0.45 (0.22, 0.93)**	0%	haloperidol
Dyspepsia[46]	1	310	0.99 (0.35, 2.78)	NE	ND
Hematology					
Agranulocytosis[46]	1	310	NE	NE	ND
Leucopenia[68]	1	448	0.32 (0.03, 3.10)	NE	ND

Table 138. Evidence summary table: haloperidol versus quetiapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Hepato-biliary					
Elevated liver transaminases[68]	1	448	0.14 (0.02, 1.12)	NE	ND
Metabolic					
HDL (low)[91]	1	207	0.76 (0.27, 2.11)	NE	ND
Hypercholesterolemia[91]	1	207	1.24 (0.63, 2.45)	NE	ND
Hyperglycemia[91]	1	207	0.67 (0.25, 1.82)	NE	ND
Hypertriglyceridemia[91]	1	207	1.19 (0.56, 2.54)	NE	ND
Ophthalmology					
Blurred vision[123]	1	25	3.23 (0.14, 72.46)	NE	ND
Sleep					
Insomnia[46,68,115,123]	4	984	1.12 (0.71, 1.76)	29%	ND
Systemic AE					
Headache[46,68,115,123]	4	984	1.31 (0.86, 1.98)	5%	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; HDL = high density lipoprotein; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Risperidone

Table 139. Evidence summary table: haloperidol versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
AE resolved spontaneously by 24hrs[151]	1	124	1.06 (0.60, 1.86)	NE	ND
Incidence of patients with AEs[72,73,81,85,117,128,136,151]	8	1313	**1.20 (1.01, 1.42)**	84%	risperidone
Mortality (Cohort)[163]	1	63352	**1.70 (1.31, 2.20)**	NE	risperidone
Serious AEs[52]	1	41	NE	NE	ND
Withdrawals due to AEs[52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151]	23	4421	**1.27 (1.04, 1.55)**	0%	risperidone

Significant results are in bold; AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 140. Evidence summary table: haloperidol versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Abnormal thinking[101]	1	255	0.61 (0.25, 1.51)	NE	ND
Accommodation disturbances[120,149]	2	1403	1.37 (0.99, 1.89)	0%	ND
Agitation[61,72,81,101]	4	916	1.30 (0.96, 1.76)	7%	ND
Anxiety[61,81,101]	3	551	0.95 (0.67, 1.34)	67%	ND
Asthenia[52,71,117,120,149]	5	1596	**1.20 (1.02, 1.41)**	0%	risperidone
Concentration difficulty[64,71,117,120]	4	1556	1.18 (0.97, 1.43)	65%	ND
Decreased appetite[64]	1	42	0.55 (0.25, 1.20)	NE	ND
Depression[101,118]	2	544	0.63 (0.34, 1.16)	0%	ND
Deterioration[73]	1	126	NE	NE	ND
Drug overdose[118]	1	289	0.33 (0.01, 7.95)	NE	ND
Decreased sexual desire[120,149]	2	1403	1.07 (0.72, 1.59)	0%	ND
Fatigue[60,64]	2	104	1.00 (0.63, 1.60)	0%	ND
Hallucination[101]	1	255	1.00 (0.49, 2.02)	NE	ND
Increased appetite[64]	1	42	1.20 (0.43, 3.33)	NE	ND
Manic reaction[128]	1	105	6.87 (0.36, 129.81)	NE	ND
Nervousness[101]	1	255	1.20 (0.68, 2.14)	NE	ND
Paranoia[101]	1	255	1.16 (0.54, 2.52)	NE	ND
Sexual disturbances[52]	1	41	0.35 (0.02, 8.10)	NE	ND
BMI and weight					
Weight gain[101]	1	255	**0.19 (0.05, 0.81)**	NE	haloperidol
Cardiovascular					
ECG abnormalities[128]	1	105	1.31 (0.31, 5.56)	NE	ND
Hypotension[61]	1	113	1.41 (0.06, 33.44)	NE	ND
Orthostatic tachycardia[61]	1	113	0.60 (0.03, 11.27)	NE	ND
Orthostatic hypotension[52,61,64]	3	196	0.76 (0.39, 1.48)	0%	ND
Palpitation[52,64]	2	83	1.18 (0.44, 3.13)	0%	ND
Cholinergic and anticholinergic					
Decreased salivation[71]	1	117	2.54 (0.69, 9.35)	NE	ND
Dry mouth[52,60,64,101]	4	400	1.44 (0.89, 2.33)	0%	ND
Hypersalivation[85]	1	77	0.15 (0.01, 2.89)	NE	ND
CNS					
Dizziness[101,128,151]	3	484	1.20 (0.72, 1.99)	22%	ND
Sedation[64]	1	42	0.87 (0.56, 1.33)	NE	ND
Somnolence[52,53,101,128,151]	5	549	1.09 (0.79, 1.50)	0%	ND
Vertigo[52,64]	2	83	0.56 (0.23, 1.38)	63%	ND
Endocrine (prolactin - thyroid)					
Amenorrhea[64,71,120,149]	4	1562	1.17 (0.80, 1.71)	0%	ND
Galactorrhea[132]	1	555	0.08 (0.00, 1.36)	NE	ND
EPS					
Akathisia[52,60,71,101,139,146,149]	7	619	**1.79 (1.31, 2.44)**	0%	risperidone
Dystonia[60,139,149]	3	139	1.01 (0.41, 2.50)	19%	ND
EPS[61,117,128,138,151]	5	675	**1.86 (1.46, 2.36)**	0%	risperidone
Oculogyric crisis[85]	1	77	0.15 (0.01, 2.89)	NE	ND
Tremor[52,85,101,128]	4	478	**2.09 (1.23, 3.53)**	0%	risperidone
Genital, urinary, and breast					
Breast tension[64]	1	42	4.00 (0.49, 32.87)	NE	ND
Dry vagina[149]	1	41	0.53 (0.11, 2.56)	NE	ND
Ejaculatory dysfunction[64,71,120,149]	4	1562	0.68 (0.43, 1.07)	0%	ND
Erectile dysfunction[64,71,120]	3	1521	1.19 (0.83, 1.70)	18%	ND
Gynecomastia[132]	1	555	0.14 (0.01, 2.76)	NE	ND
Micturition disturbances[52]	1	41	NE	NE	ND

Table 140. Evidence summary table: haloperidol versus risperidone – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
GI					
Constipation[52,53,64,101,120,128,149]	7	1870	1.04 (0.78, 1.38)	35%	ND
Diarrhea[101]	1	255	1.36 (0.72, 2.57)	NE	ND
Dyspepsia[128]	1	105	0.98 (0.42, 2.27)	NE	ND
Nausea/Vomiting[53,61,64,85,101]	5	511	1.17 (0.74, 1.87)	0%	ND
Hematology					
Agranulocytosis[145]	1	78	NE	NE	ND
Ophthalmology					
Blurred vision[60,64]	2	104	0.47 (0.17, 1.30)	40%	ND
Respiratory and airway					
Rhinitis[101]	1	255	1.00 (0.60, 1.67)	NE	ND
Sleep					
Insomnia[52,61,81,101,120,151]	6	2078	1.03 (0.85, 1.26)	10%	ND
Sleep disorder[52,85]	2	118	2.47 (0.90, 6.76)	33%	ND
Systemic AE					
Headache[52,53,61,64,81,85,101,128,151]	9	964	0.83 (0.63, 1.08)	0%	ND
Increased sweating[52,64]	2	83	1.54 (0.59, 3.99)	41%	ND
Infection[53]	1	24	7.00 (0.40, 122.44)	NE	ND
Pain[101]	1	255	0.48 (0.21, 1.06)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I^2 = I–squared; ND = no difference; NE = not estimable

Haloperidol Versus Ziprasidone

Table 141. Evidence summary table: haloperidol versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[57,69,73,83,86,144]	6	1448	**1.13 (1.03, 1.23)**	31%	ziprasidone
Mortality[116,144]	2	408	3.10 (0.13, 75.68)	NE	ND
Serious AEs[57,86,91,144]	4	1403	1.02 (0.60, 1.75)	0%	ND
Withdrawals due to AEs[57,83,86,91,116,144]	6	1551	**1.73 (1.30, 2.32)**	0%	ziprasidone

Significant results are in bold; AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 142. Evidence summary table: haloperidol versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[86,116]	2	359	1.05 (0.66, 1.68)	0%	ND
Anxiety[86,116,144]	3	709	1.42 (0.77, 2.61)	15%	ND
Asthenia[86,116]	2	359	0.63 (0.29, 1.35)	0%	ND
Depression[86,144]	2	651	1.52 (0.84, 2.76)	0%	ND
Deterioration[73]	1	120	2.90 (0.12, 69.87)	NE	ND
Hallucinations[86]	1	301	1.29 (0.56, 2.97)	NE	ND
BMI and weight					
Overweight[91]	1	185	0.91 (0.47, 1.75)	NE	ND
Weight gain[91,144]	2	535	0.86 (0.45, 1.67)	47%	ND
Weight loss[144]	1	350	0.23 (0.05, 1.05)	NE	ND
Cardiovascular					
Cardiovascular AEs[116]	1	58	NE	NE	ND
ECG abnormalities[57,86,91,116,122,144]	6	2060	0.84 (0.53, 1.31)	0%	ND
Hypertension[116]	1	58	3.43 (0.15, 80.83)	NE	ND
Hypotension[116]	1	58	0.57 (0.06, 5.99)	NE	ND

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Syncope[116]	1	58	NE	NE	ND

Table 143. Evidence summary table: haloperidol versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Cholinergic and anticholinergic					
Dry mouth[86,116]	2	359	1.20 (0.38, 3.84)	29%	ND
CNS					
Dizziness[86,116,144]	3	709	1.19 (0.43, 3.34)	55%	ND
Hypokinesia[144]	1	350	**6.21 (1.41, 27.34)**	NE	ziprasidone
Hypotonia[144]	1	350	**5.86 (1.75, 19.65)**	NE	ziprasidone
Somnolence[57,86,116,122,144]	5	1875	0.89 (0.70, 1.12)	36%	ND
Dermatology					
Injection-site pain[116]	1	58	0.57 (0.06, 5.99)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia[57,91]	2	752	1.53 (0.46, 5.05)	89%	ND
EPS					
Akathisia[57,86,91,116,122,144]	6	2060	1.58 (1.00, 2.50)	80%	ND
Dyskinesia[91]	1	185	3.99 (0.19, 81.98)	NE	ND
Dystonia[57,91,144]	3	1102	**2.19 (1.34, 3.60)**	15%	ziprasidone
EPS[57,69,116,122,144]	5	1594	**2.34 (1.56, 3.53)**	63%	ziprasidone
Hypertonia[57,86,116]	3	926	**2.45 (1.52, 3.94)**	0%	ziprasidone
Movement disorder[86]	1	301	**2.73 (1.77, 4.19)**	NE	ziprasidone
Parkinsonism[91]	1	185	1.81 (0.95, 3.46)	NE	ND
Psychosis[86]	1	301	0.48 (0.15, 1.57)	NE	ND
Tardive dyskinesia[86]	1	301	4.84 (0.23, 99.93)	NE	ND
Tremor[57,86,116,122,144]	5	1875	**2.55 (1.79, 3.63)**	4%	ziprasidone
GI					
Dyspepsia[144]	1	350	0.38 (0.12, 1.16)	NE	ND
Nausea/Vomiting[86,116]	2	359	0.55 (0.27, 1.11)	0%	ND
Metabolic					
HDL (low)[91]	1	185	0.96 (0.30, 3.02)	NE	ND
Hypercholesterolemia[91]	1	185	0.75 (0.40, 1.39)	NE	ND
Hyperglycemia[91]	1	185	0.68 (0.24, 1.95)	NE	ND
Hypertriglyceridemia[91]	1	185	1.03 (0.48, 2.24)	NE	ND
Ophthalmology					
Abnormal vision[116]	1	58	5.71 (0.29, 114.05)	NE	ND
Sleep					
Insomnia[57,86,116,122]	4	1525	0.81 (0.63, 1.04)	0%	ND
Systemic AE					
Headache[86,116,144]	3	709	0.49 (0.11, 2.18)	82%	ND
Malaise[116]	1	58	0.38 (0.04, 3.47)	NE	ND
Sweating[116]	1	58	5.71 (0.29, 114.05)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CN = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; HDL = high density lipoprotein; I^2 = I–squared; ND = no difference; NE = not estimable

Perphenazine Versus Aripiprazole

Table 144. Evidence summary table: perphenazine versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Serious AEs[93]	1	300	0.79 (0.49, 1.28)	NE	ND
Withdrawals due to AEs[93]	1	300	0.53 (0.27, 1.05)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 145. Evidence summary table: perphenazine versus aripiprazole – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Agitation[93]	1	300	1.01 (0.61, 1.69)	NE	ND
Anxiety[93]	1	300	1.19 (0.63, 2.24)	NE	ND
Dizziness[93]	1	300	**5.27 (1.18, 23.66)**	NE	aripiprazole
Psychosis[93]	1	300	0.82 (0.42, 1.59)	NE	ND
Cardiovascular					
ECG abnormalities[93]	1	300	**15.82 (2.12, 118.27)**	NE	aripiprazole
CNS					
Somnolence[93]	1	300	2.64 (0.85, 8.22)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia[93]	1	300	**13.89 (6.25, 30.86)**	NE	aripiprazole
EPS					
Akathisia[93]	1	300	2.29 (0.89, 5.85)	NE	ND
EPS[93]	1	300	1.90 (0.65, 5.53)	NE	ND
GI					
Dyspepsia[93]	1	300	0.59 (0.27, 1.30)	NE	ND
Metabolic					
Abnormal total creatinine phoshpokinase value[93]	1	300	0.62 (0.25, 1.52)	NE	ND
Increased creatinine phosphokinase[93]	1	300	0.47 (0.15, 1.49)	NE	ND
Sleep					
Insomnia[93]	1	300	0.86 (0.56, 1.31)	NE	ND
Systemic AE					
Headache[93]	1	300	0.55 (0.29, 1.03)	NE	ND
Injury[93]	1	300	**4.75 (1.04, 21.60)**	NE	aripiprazole

Significant results are in bold; AE = adverse event; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I2 = I–squared; ND = no difference; NE = not estimable

Perphenazine Versus Olanzapine

Table 146. Evidence summary table: perphenazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[23]	1	597	0.93 (0.83, 1.04)	NE	ND
Serious AEs[23]	1	597	1.17 (0.72, 1.88)	NE	ND
Withdrawals due to AEs[23]	1	597	0.83 (0.58, 1.19)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 147. Evidence summary table: perphenazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Suicide attempt[23]	1	597	0.64 (0.06, 7.06)	NE	ND
Suicidal ideation[23]	1	597	3.86 (0.40, 36.91)	NE	ND
BMI and weight					
Weight gain[23]	1	597	**0.41 (0.28, 0.60)**	NE	perphenazine
Cardiovascular					
ECG abnormalities[23]	1	597	6.43 (0.31, 133.39)	NE	ND
Hypertension[23]	1	597	0.85 (0.51, 1.40)	NE	ND
Orthostatic hypotension[23]	1	597	1.20 (0.75, 1.95)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities[23]	1	597	0.82 (0.32, 2.08)	NE	ND
EPS					
AIMS global severity score ≥2[23]	1	597	**1.65 (1.07, 2.54)**	NE	olanzapine
BARS global score ≥ 3[23]	1	597	1.37 (0.69, 2.73)	NE	ND
Dystonia[23]	1	597	1.29 (0.08, 20.48)	NE	ND
SAS mean score ≥1[23]	1	597	0.84 (0.45, 1.58)	NE	ND
Genital, urinary, and breast					
Gynecomastia/galactorrhea[23]	1	597	0.74 (0.22, 2.49)	NE	ND
Incontinence, nocturia[23]	1	597	0.43 (0.17, 1.07)	NE	ND
Metabolic					
Diabetes[23]	1	597	0.81 (0.45, 1.45)	NE	ND
Metabolic syndrome[23]	1	597	0.88 (0.63, 1.21)	NE	ND
Ophthalmology					
Cataracts[23]	1	597	0.43 (0.04, 4.10)	NE	ND
Sleep					
Hypersomnia[23]	1	597	0.92 (0.71, 1.18)	NE	ND
Insomnia[23]	1	597	**1.54 (1.12, 2.13)**	NE	olanzapine

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I^2 = I–squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Quetiapine

Table 148. Evidence summary table: perphenazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[23]	1	598	1.00 (0.89, 1.12)	NE	ND
Serious AEs[23]	1	598	1.17 (0.73, 1.88)	NE	ND
Withdrawals due to AEs[23]	1	598	1.05 (0.72, 1.55)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 149. Evidence summary table: perphenazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Suicidal ideation[23]	1	598	1.94 (0.33, 11.51)	NE	ND
Suicide attempt[23]	1	598	1.29 (0.08, 20.55)	NE	ND
BMI and weight					
Weight gain[23]	1	598	0.76 (0.50, 1.17)	NE	ND
Cardiovascular					
ECG abnormalities[23]	1	598	0.43 (0.09, 2.12)	NE	ND
Hypertension[23]	1	598	0.80 (0.49, 1.32)	NE	ND
Orthostatic hypotension[23]	1	598	0.99 (0.62, 1.55)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects[23]	1	598	0.70 (0.53, 0.93)	NE	perphenazine
Endocrine (prolactin - thyroid)					
Menstrual irregularities[23]	1	598	1.81 (0.58, 5.63)	NE	ND
EPS					
AIMS global severity score ≥2[23]	1	598	1.76 (1.13, 2.75)	NE	quetiapine
BARS global score ≥3[23]	1	598	1.29 (0.66, 2.53)	NE	ND
Dystonia[23]	1	598	1.29 (0.08, 20.55)	NE	ND
SAS mean score ≥1[23]	1	598	1.61 (0.77, 3.39)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea[23]	1	598	0.86 (0.25, 3.02)	NE	ND
Incontinence/nocturia[23]	1	598	0.52 (0.20, 1.31)	NE	ND
Metabolic					
Diabetes[23]	1	598	1.57 (0.79, 3.12)	NE	ND
Metabolic syndrome[23]	1	598	1.19 (0.84, 1.70)	NE	ND
Ophthalmology					
Cataracts[23]	1	598	1.29 (0.08, 20.55)	NE	ND
Sleep					
Hypersomnia[23]	1	598	0.93 (0.72, 1.19)	NE	ND
Insomnia[23]	1	598	1.37 (1.01, 1.87)	NE	ND

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I^2 = I–squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Risperidone

Table 150. Evidence summary table: perphenazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[23]	1	602	0.96 (0.85, 1.07)	NE	ND
Serious AEs[23]	1	602	1.15 (0.72, 1.84)	NE	ND
Withdrawals due to AEs[23]	1	602	1.54 (1.00, 2.36)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 151. Evidence summary table: perphenazine versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Suicidal ideation[23]	1	602	0.98 (0.22, 4.34)	NE	ND
Suicide attempt[23]	1	602	0.65 (0.06, 7.17)	NE	ND
BMI and weight					
Weight gain[23]	1	602	0.90 (0.58, 1.41)	NE	ND
Cardiovascular					
ECG abnormalities[23]	1	602	0.37 (0.08, 1.78)	NE	ND
Hypertension[23]	1	602	0.94 (0.56, 1.57)	NE	ND
Orthostatic hypotension[23]	1	602	1.02 (0.65, 1.62)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects[23]	1	602	0.89 (0.66, 1.19)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities[23]	1	602	0.57 (0.24, 1.37)	NE	ND
EPS					
AIMS global severity score ≥2[23]	1	602	1.41 (0.93, 2.13)	NE	ND
BARS global score ≥3[23]	1	602	1.05 (0.55, 1.98)	NE	ND
Dystonia[23]	1	602	0.65 (0.06, 7.17)	NE	ND
SAS mean score ≥1[23]	1	602	0.85 (0.45, 1.60)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea[23]	1	602	0.37 (0.12, 1.12)	NE	ND
Incontinence/ nocturia[23]	1	602	0.31 (0.13, 0.75)	NE	perphenazine
Metabolic					
Diabetes[23]	1	602	1.06 (0.57, 1.96)	NE	ND
Metabolic syndrome[23]	1	602	1.42 (0.98, 2.06)	NE	ND
Ophthalmology					
Cataracts[23]	1	602	0.65 (0.06, 7.17)	NE	ND
Sleep					
Hypersomnia[23]	1	602	1.01 (0.78, 1.30)	NE	ND
Insomnia[23]	1	602	1.04 (0.79, 1.37)	NE	ND

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I^2 = I–squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Ziprasidone

Table 152. Evidence summary table: perphenazine versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Incidence of patients with AEs[23]	1	446	1.01 (0.88, 1.16)	NE	ND
Serious AEs[23]	1	446	1.08 (0.63, 1.87)	NE	ND
Withdrawals due to AEs[23]	1	446	1.01 (0.65, 1.58)	NE	ND

AE = adverse event; I^2 = I–squared; ND = no difference; NE = not estimable

Table 153. Evidence summary table: perphenazine versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Behavior and psychosis					
Suicidal ideation[23]	1	446	1.06 (0.18, 6.30)	NE	ND
Suicide attempt[23]	1	446	0.71 (0.04, 11.26)	NE	ND
BMI and weight					
Weight gain[23]	1	446	1.71 (0.90, 3.27)	NE	ND
Cardiovascular					
ECG abnormalities[23]	1	446	0.71 (0.10, 4.99)	NE	ND
Hypertension[23]	1	446	0.65 (0.38, 1.11)	NE	ND
Orthostatic hypotension[23]	1	446	0.86 (0.52, 1.42)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects[23]	1	446	1.09 (0.76, 1.58)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities[23]	1	446	0.62 (0.23, 1.68)	NE	ND
EPS					
AIMS global severity score ≥2[23]	1	446	1.61 (0.96, 2.72)	NE	ND
BARS global score ≥3[23]	1	446	0.81 (0.41, 1.62)	NE	ND
Dystonia[23]	1	446	0.24 (0.02, 2.25)	NE	ND
SAS mean score ≥1[23]	1	446	1.77 (0.70, 4.48)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea[23]	1	446	0.47 (0.14, 1.65)	NE	ND
Incontinence/ nocturia[23]	1	446	0.43 (0.16, 1.15)	NE	ND
Metabolic					
Diabetes[23]	1	446	1.00 (0.49, 2.05)	NE	ND
Metabolic syndrome[23]	1	446	1.51 (0.96, 2.39)	NE	ND
Ophthalmology					
Cataracts[23]	1	446	2.13 (0.09, 51.99)	NE	ND
Sleep					
Hypersomnia[23]	1	446	1.17 (0.85, 1.60)	NE	ND
Insomnia[23]	1	446	0.84 (0.62, 1.13)	NE	ND

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I^2 = I–squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Thioridazine versus Clozapine

Table 154. Evidence summary table: thioridazine versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Mortality (Cohort)[163]	1	32280	**2.12 (1.38, 3.26)**	NE	clozapine

I2 = I–squared; NE = not estimable

Thioridazine versus Risperidone

Table 155. Evidence summary table: thioridazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I^2	Less with
Mortality (Cohort)[163]	1	46007	**1.82 (1.37, 2.40)**	NE	risperidone

I2 = I–squared; NE = not estimable

Appendix O. First-Generation and Second-Generation FDA-Approved and Available Antipsychotics

Table O–1. First-generation antipsychotics included in the CER

Generic name	Trade names(s)	Mode of administration	Recommended dose	Frequency
Chlorpromazine	Chlorpromazine hydrochloride Chlorpromazine hydrochloride	Oral IM/IV	200-600 mg/day	1-4 times
Droperidol	Inapsine	IM/IV	Initial 2.5 mg/dose	increase by 1.25 mg as needed
Fluphenazine	Fluphenazine decanoate Fluphenazine hydrochloride	Oral IM	2.5-10 mg/day 2.5-10 mg/dose	3-4 times every 6 to 8 hour
Haloperidol	Haloperidol Haldol Haloperidol decanoate	Oral Tablets Solution IM (as lactate)	4-12 mg/day	1-2 times 2-3 times Every hour if needed
Loxapine	Loxapine, Loxapine succinate	Oral	60-100 mg/day	2-4 times
Perphenazine	Perphenazine	Oral (non-hospitalized) Oral (hospitalized)	12-18 mg/day; 16-64 mg/day	3 times 2-4 times
Pimozide	ORAP	Oral	7-10 mg/day	1-3 times
Prochlorperazine	Compro Prochlorperazine Prochlorperazine edisylate Prochlorperazine maleate	Oral IM IV	15-40 mg/day 15-40 mg/day 7.5-40 mg/day	3-4 times 3-4 times 3-4 times
Thioridazine	Thioridazine hydrochloride D/C: Thioridazine hydrochloride intensol, Mellaril, Mellaril-S	Oral	150-300 mg/day	2-3 times
Thiothixene	Navane Thiothixene D/C : Thiothixene hydrochloride, Thiothixene hydrochloride intensol	Oral	6-30 mg/day	2-3 times
Trifluoperazine	Trifluoperazine hydrochloride	Oral (non-hospitalized)	1-2 mg	2 times/day

D/C = discontinued according to FDA site; IM = intramuscular; IV = intravenous; mg = milligrams

Table O–2. Second-generation antipsychotics included in the CER

Generic name	Brand names(s)	Mode of administration	Recommended dose	Frequency
Aripiprazole	Abilify	Tablet Solution Orally disintegrating tablet Injection	10-15mg/day; Max 30mg/day	QD ≥2 hour between doses
Asenapine	Saphouris	Orally disintegrating tablet	Schizophrenia 5mg; BD 10mg	2 times/day 2 times/day
Clozapine	Clozapine Clozaril	Tablet Orally disintegrating tablet	300-450 mg/day	1-3 times/day
Iloperidone	Fanapt	Tablet	12-24mg/day	2 times/day
Olanzapine	Olanzapine Zyprexa, Zyprexa Zydis	Tablet Orally disintegrating tablet IM injection	Schizophrenia, 10mg/day; BD I 10-15mg/day	QD QD
Lurasidone	Latuda	Tablet	40-80mg/day	1-2 times/day
Paliperidone	Invega Invega sustenna	Tablet extended release IM injection	6mg/day 39-234 mg/day	QD in the AM
Quetiapine	Quetiapine fumarate Seroquel Seroquel XR	Tablet Sustained release tablets	Schizophrenia, 150-750mg/day; BD (mania), 400-800mg/day; BD (depression), 300mg/day; BD (maintenance), 400-800mg/day	2 times/day 2 times/day 2 times/day 2 times/day QD at bedtime 2 times/day
Risperidone	Risperidone, Risperdal, Risperdal consta	Tablet Solution Orally disintegrating tablet IM injection	Schizophrenia, 4-8mg/day; BD (mania), 1-6mg/day 25 mg/day	1-2 times/day
Ziprasidone	Ziprasidone hydrochloride Geodon	Capsules IM injection	Schizophrenia, up to 80mg; BD (manic/mixed, maintenance), 40-80mg; Agitation associated with Schizophrenia (IM), up to max 40mg/day	2 times/day 2 times/day 10mg may be injected q2 hour

BD = bipolar disease; IM = intramuscular; mg = milligrams; QD = every day; q2 = every two hours

Table O–3. First-generation antipsychotics: FDA status

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Chlorpromazine	Approved 1974	Schizophrenia BP (mania) Hyperactivity Uncontrolled hiccups, nausea and vomiting	Adults Children (1-12 yrs)	Patients with cardiovascular disease or hx of seizures
Droperidol	Approved 1988	Antiemetic Acute psychosis	Adults Children (2-12 yrs) as antiemetic, no data on pediatric psychosis	QT prolongation (dose related) Torsades de pointes
Fluphenazine	Approved 1960	Schizophrenia BD (mania)	Adults Children >12yrss Not recommended for use in children under 12 yrs	Possible increased mortality in elderly with dementia-related psychosis Not approved for the treatment of dementia-related behavior problems.
Haloperidol	Approved 1986	Schizophrenia Tourette's Disorder	Adults Safety and effectiveness in pediatric patients <18 yrs have not been established	Increased mortality in elderly with dementia-related psychosis
Loxapine	Approved 1975	Schizophrenia	Adults Safety and effectiveness in pediatric patients <16 have not been established	Increased mortality in elderly with dementia-related psychosis
Perphenazine	Approved 1965	Schizophrenia	Adults Safety and effectiveness in pediatric patients have not been established	Increased mortality in elderly with dementia-related psychosis Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking

Table O–3. First-generation antipsychotics: FDA status (continued)

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Pimozide	Approved 1984	Tourette's Disorder	Children and adults 8-53 yrs. Limited evidence in children <12 yrs Use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder	Use of pimozide in tx of Tourette's Disorder involves different risk/benefit considerations than tx of other conditions. A decision to use ORAP should take into consideration Tardive Dyskinesia Neuroleptic Malignant Syndrome (NMS) Sudden, unexpected deaths in conditions other than Tourette's Disorder. May have tumorigenic potential.
Thiothixene	Approved 1967	Schizophrenia	Adults Safety and effectiveness in pediatric patients <12 years have not been established	Increased mortality in elderly with dementia-related psychosis
Trifluoperazine	Approved 1959	Schizophrenia	Adults and children (6-12 yrs)	Increased mortality in elderly patients with dementia-related psychosis
Prochlorperazine	Approved 1956	Schizophrenia Severe nausea and vomiting	Adults and children Children >2 yrs and >20 pounds	May cause tardive dyskinesia
Thioridazine	Approved 1962	Schizophrenia	Adults and children	Life-threatening pro-arrhythmic effect

BD = bipolar disease; IM = intramuscular; tx = treatment; yrs = years

Table O–4. Second-generation antipsychotics: FDA status

Drug	FDA status	Indications	Age group approved for	Black box warnings
Aripiprazole	Approved 2002	Schizophrenia	Adults & adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	Approved 2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults & pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking & behavior
	Approved 2007	Adjunctive tx of major depressive disorder	Adults Children (6-17 yrs) Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	Leukopenia, Neutropenia, Agranulocytosis Not approved for behavior problems in older adults with dementia.
	Approved 2009	Autistic Disorder, Injection		
Aripiprazole	Approved 2002	Schizophrenia	Adults and adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	Approved 2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking and behavior
	Approved 2007	Adjunctive tx of major depressive disorder	Adults	Not approved for behavior problems in older adults with dementia.
		Injection	Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	
Asenapine	Approved 2009	Acute Schizophrenia BD I (manic/mixed)	Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Clozapine,	Approved 1989 Approved 2002	Treatment resistant Schizophrenia Reduce the risk of suicidal behavior in younger schizophrenics.	Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	1. agranulocytosis 2. seizures 3. myocarditis 4. cardiovascular and respiratory effects, (respiratory and/or cardiac arrest). 5. increased mortality in elderly patients with dementia-related psychosis
Iloperidone	Approved 2009	Acute Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.

BD = bipolar disease; tx = treatment; yrs = years

Table O–4. Second-generation antipsychotics: FDA status (continued)

Drug	FDA status	Indications	Age group approved for	Black box warnings
Lurasidone	Approved 2010	Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis
Olanzapine	Approved 1996	Schizophrenia &BD(L) (manic/mixed)	Adults Adolescents (13-17 yrs),	Increased mortality in elderly with dementia-related psychosis
	Approved 2003: combined w fluoxetine	BD (depressive)	Schizophrenia & BD (manic/ mixed)	Not approved for patients with dementia-related psychosis.
	Approved 2004	BD(L) long-term tx	Pediatric use: safety & effectiveness not established in patients <13 yrs	
	Approved 2009: combined w fluoxetine	Tx resistant depression		
Paliperidone	Approved 2006	Schizophrenia Schizoaffective disorder	Adult Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Quetiapine	Approved 1997	Schizophrenia	Adults & adolescents (13-17 yrs) Adults, children & adolescents (10-17 yrs)	Increased mortality in elderly with dementia-related psychosis Increased risk of suicidal thinking and behavior
	Approved 2004	BD (acute manic)	Adults	
	Approved 2008	BD (depression) BD (maintenance)	Adults	Not approved for patients with dementia-related psychosis
Risperidone	Approved 1993	Schizophrenia	Adults & adolescents (13-17 yrs) Adults & adolescents (10-17 years)	Increased mortality in elderly with dementia-related psychosis
	Approved 2007	BD (manic/mixed)	Children (5-16 yrs)	
	Approved 2003	Irritability associated with autism		
Ziprasidone	Approved 2001	Schizophrenia BD (manic/mixed) BD (maintenance)	Adults Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis