



Effective Health Care Program

Comparative Effectiveness Review
Number 43

Off-Label Use of Atypical Antipsychotics: An Update



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Off-Label Use of Atypical Antipsychotics: An Update

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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 <http://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 the Task Order Officer named below 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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Off-Label Use of Atypical Antipsychotics: An Update

Structured Abstract

Objectives. Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia, bipolar disorder, and for some drugs, depression. We performed a systematic review on the efficacy and safety of atypical antipsychotic drugs for use in conditions lacking FDA approval.

Data Sources. We searched PubMed, Embase, PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane DARE (Database of Abstracts of Reviews of Effects), and Cochrane CENTRAL (Cochrane Central Register of Controlled Trials) from inception to May 2011. We included only English-language studies.

Review Methods. Controlled trials comparing an atypical antipsychotic (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, paliperidone) to either placebo, another atypical antipsychotic drug, or other pharmacotherapy, for the off-label conditions of anxiety disorder, attention deficit hyperactivity disorder, dementia and severe geriatric agitation, major depressive disorder, eating disorders, insomnia, obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome were included. Observational studies with sample sizes greater than 1,000 were included to assess rare adverse events. Two investigators conducted independent article review, data abstraction, and study quality assessment.

Results. One hundred seventy trials contributed data to the efficacy review. Among the placebo-controlled trials of elderly patients with dementia reporting a total/global outcome score that includes symptoms such as psychosis, mood alterations, and aggression, small but statistically significant effect sizes ranging from 0.12 and 0.20 were observed for aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, pooled analysis of three large trials showed that quetiapine was associated with a 26 percent greater likelihood of "responding," defined as at least 50 percent improvement on the Hamilton Anxiety Scale, compared with placebo. For obsessive-compulsive disorder, risperidone was associated with a 3.9-fold greater likelihood of "responding," defined as a 25 to 35 percent improvement on the Yale Brown Obsessive Compulsive Scale (YBOCS) compared with placebo.

We identified 6 trials on eating disorders, 12 on personality disorder, an existing meta-analysis and 10 trials of risperidone or olanzapine for PTSD, 36 trials for depression of which 7 assessed drugs without an FDA-approved indication, and 33 trials of aripiprazole, olanzapine, quetiapine, or risperidone for treating substance abuse disorders. We identified one small trial (N=13) of atypical antipsychotics for insomnia which was inconclusive. For eating disorder patients specifically, evidence shows that atypicals do not cause significant weight gain. The level of evidence is mixed regarding personality disorders and moderate for an association of risperidone with improving post-traumatic stress disorder. Evidence does not support efficacy of atypical antipsychotics for substance abuse.

In elderly patients, adverse events included an increased risk of death (number needed to harm [NNH]=87), stroke (for risperidone, NNH=53), extrapyramidal symptoms (for olanzapine (NNH=10) and risperidone (NNH=20), and urinary symptoms (NNH= from 16 to 36). In non-elderly adults, adverse events included weight gain (particularly with olanzapine), fatigue,

sedation, akathisia (for aripiprazole) and extrapyramidal symptoms. Direct comparisons of different atypical antipsychotics for off-label conditions are rare.

Conclusions. Benefits and harms vary among atypical antipsychotics for off-label usage. For symptoms associated with dementia in elderly patients, small but statistically significant benefits were observed for aripiprazole, olanzapine, and risperidone. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder, and risperidone was associated with benefits in the treatment of OCD; however, adverse events were common.

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Executive Summary

Background

Antipsychotics medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These medications are commonly divided into two classes, reflecting two waves of historical development: the conventional antipsychotics and the atypical. The conventional antipsychotics served as the first successful pharmacologic treatment for primary psychotic disorders such as schizophrenia. Having been widely used for decades, the conventional antipsychotics also produced various side effects requiring additional medications, which spurred the development of the atypical antipsychotics.

Currently, nine atypical antipsychotic drugs have been approved by FDA: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. These drugs have been used off-label (i.e., for indications not approved by FDA) for the treatment of various psychiatric conditions. While it is legal for a physician to prescribe drugs in such a manner, it is illegal for the manufacturer to actively promote such use.

A 2006 study on Efficacy and Comparative Effectiveness of Off-label Use of Atypical Antipsychotics reviewed the scientific evidence on the safety, efficacy, and effectiveness for off-label uses. (Clozapine was excluded because of its association with a potentially fatal blood disorder of bone marrow suppression, and it requires frequent blood tests for safety monitoring.) The 2006 study examined 84 published studies on atypicals and found that the most common off-label uses of the drugs were for treatment of depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), personality disorders, Tourette's syndrome, autism, and agitation in dementia. It concluded that with few exceptions, there was insufficient high-strength evidence to reach conclusions about the efficacy of any off-label uses of these medications. It also found strong evidence that atypicals are associated with increased risk of adverse events such as significant weight gain, sedation, and, among the elderly, increased mortality. Future research areas suggested by the report include safe treatment for agitation in dementia, association between the increased risk of death and antipsychotics drugs, and comparison of the development of adverse effects between patients taking atypical antipsychotics and those taking conventional antipsychotics.

Since publication of that report, important changes have occurred that make the report out of date. Studies have been published on new off-label uses, such as treatment of eating disorders, insomnia, attention-deficit hyperactivity disorder (ADHD), anxiety, and substance abuse. New or increased adverse effects of off-label indications have been observed and new atypicals (asenapine, iloperidone, and paliperidone) have been approved by FDA for the treatment of schizophrenia and bipolar disorder. In addition, the following previously off-label uses have been approved for on-label use by the FDA:

- Quetiapine and quetiapine ER (extended release) as monotherapy in bipolar depression
- Quetiapine ER as augmentation for major depressive disorder (MDD)
- Aripiprazole as augmentation for MDD
- Olanzapine/fluoxetine combination for MDD
- Olanzapine/fluoxetine combination for bipolar depression
- Risperidone and aripiprazole for autism spectrum disorders

An update is needed to better understand the trends in off-label use and the associated risks and benefits. Further, a number of issues remain unclear due to insufficient information in the previous report: subpopulations (i.e., race/ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. This update will try to address these issues.

This report covers the following off-label uses of atypical antipsychotic medications: anxiety, ADHD, dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. Autism, included in the original systematic review, is now reviewed in a study on the comparative effectiveness of typical and atypical antipsychotics for on-label indications, conducted by another organization.

This report addresses the following Key Questions:

Key Question 1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question 2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

Sub-Key Question 2. How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question 5. What is the effective dose and time limit for off-label indications?

Conclusions

Key Question 1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.

Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.

One recent study indicated that the 2005 regulatory warning from the FDA and Health Canada was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients.

Use of atypicals in the elderly is much higher in long-term care settings than in the community. Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs health system.

At least 90 percent of antipsychotics prescribed to children are atypical, rather than conventional antipsychotics. The majority of use is off-label.

No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.

Key Question 2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics, for off-label indications? Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

The efficacy results are summarized in Table A. It is important to note that no trials of the three most recently FDA-approved atypicals (asenapine, iloperidone, and paliperidone) were found for off-label use. Cells shaded in green indicate areas with the strongest evidence of efficacy, followed by the areas in blue. White areas containing circles indicate areas where no clinical trials exist. Brown and pink areas indicate areas where evidence of inefficacy exists.

Table B shows how our current efficacy findings compare with those of our original Comparative Effectiveness Review (CER) submitted to the Agency for Healthcare Research and Quality (AHRQ) in 2006. The evidence that atypicals have efficacy in treating symptoms of dementia has increased in the past few years; this evidence must be weighed against possible harms described in Key Question 4 below. Evidence of efficacy as augmentation for MDD and OCD patients who have not responded adequately to selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) has also increased. Table B is organized as follows: First, all conditions dealt with in our original CER, in alphabetical order; second, all the new off-label indications in alphabetical order.

Table A. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety					
- generalized anxiety disorder	O	-	++	-	-
Anxiety					
- social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder					
-no co-occurring disorders	O	O	O	+	O
Attention Deficit/Hyperactivity Disorder					
-bipolar children	-	O	O	O	O
Attention Deficit/Hyperactivity Disorder					
-mentally retarded children	O	O	O	+	O
Dementia overall	++	+	+	++	O
Dementia psychosis	+	+-	+-	++	O
Dementia agitation	+	++	+-	++	O
Depression					
-MDD augmentation of SSRI/SNRI	++	+	++	++	+
Depression					
-MDD: Monotherapy	O	-	++	O	O
Eating Disorders	O	--	-	O	O
Insomnia	O	O	-	O	O
Obsessive Compulsive Disorder					
-augmentation of SSRI	O	+	--	++	-
Obsessive Compulsive Disorder					
-augmentation of citalopram	O	O	+	+	O
Personality Disorder					
-borderline	+	+-	+	O	-
Personality Disorder					
-schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder	O	+-	+	++	O
Substance Abuse alcohol	--	-	-	O	O
Substance Abuse cocaine	O	-	O	-	O
Substance Abuse methamphetamine	-	O	O	O	O
Substance Abuse methadone clients	O	O	O	-	O
Tourette's Syndrome	O	O	O	+	-

++: moderate or high evidence of efficacy

+: low or very low evidence of efficacy

+-: mixed results

-: low or very low evidence of inefficacy

--: moderate or high evidence of inefficacy

O: no trials

[]: Approved by FDA for the indication

MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitors

Note: Symbols denote strength of evidence, not size of potential effect. For example in dementia “++” indicates moderate-to-high strength of evidence that there is a beneficial effect, however the size of the effect is small.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Dementia	High	<p>A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole.</p> <p>There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant.</p> <p>Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.</p>	<p>Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude.</p> <p>Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.</p> <p>Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI.</p> <p>Three head to head trials compared atypicals; none was found superior.</p>	<p>Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.</p>
Depression – MDD: augmentation of SSRI/SNRI	<p>Moderate - risperidone, aripiprazole, quetiapine</p> <p>Low – olanzapine, ziprasidone</p>	<p>Three trials assessed the combination of olanzapine and fluoxetine, one trial each assessed augmentation of various SRIs with risperidone, ziprasidone, and quetiapine, and one study assessed adding risperidone versus olanzapine to SSRI.</p> <p>The combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2–4 weeks) with combination therapy using olanzapine or quetiapine.</p> <p>The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.</p>	<p>We conducted a meta-analysis using “response” to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone and ziprasidone were included in two trials and one trial, respectively. These reported the drug superior to placebo.</p> <p>One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.</p>	<p>Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p>

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Depression – MDD: Monotherapy	Moderate	The three olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	In our meta-analysis of five placebo-controlled trials, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.
Obsessive-compulsive disorder – augmentation of SSRI	Moderate – risperidone Low - olanzapine	12 trials used risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy. Relative risk of “responding” significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	Our updated meta-analysis found risperidone superior to placebo, as measured by changed in the Yale Brown Obsessive Compulsive Scale (Y-BOCS). There were too few studies (two) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. One new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Risperidone has efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also have efficacy . Quetiapine is more efficacious than ziprasidone and clomipramine for this purpose.
Obsessive-compulsive disorder – augmentation of citalopram	Low- quetiapine Very low - risperidone	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared with placebo (102 days vs. 85 days)	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Post-traumatic stress disorder	Moderate – risperidone Olanzapine – Low Quetiapine – very low	Four trials of risperidone and two trials of olanzapine, each of at least 6 week duration, treated patients with PTSD. Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	Three new trials of risperidone were found, allowing us to conduct a meta-analysis using the Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A new trial found a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared with placebo. Exact scores were not reported. We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.
Personality disorders – borderline	Low – aripiprazole Very low – quetiapine, olanzapine	Three trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Aripiprazole was superior to placebo in one small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared with placebo at 12 weeks. Two new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. One new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Olanzapine had mixed results in 7 trials, aripiprazole was found efficacious in two trials, quetiapine was found efficacious in one trial, and ziprasidone was found not efficacious in one trial.
Personality disorders – schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had mixed results when used to treat schizotypal personality disorder in two small trials.
Tourette’s syndrome	Low	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared with placebo.	No additional trials.	Same as 2006: Risperidone is at least as efficacious as pimozide or clonidine for Tourette’s syndrome.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Anxiety	Moderate	Not covered.	<p>Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group.</p> <p>One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.</p>	Quetiapine has efficacy as treatment for Generalized Anxiety Disorder
Attention deficit/hyperactivity disorder – no co-occurring disorders	Low	Not covered.	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale – Parent version (CAS-P).	Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.
Attention deficit/hyperactivity disorder – mentally retarded children	Low	Not covered.	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.
Attention deficit/hyperactivity disorder – bipolar children	Low	Not covered.	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is inefficacious in reducing ADHD symptoms in children with bipolar disorder.
Eating disorders	Moderate – olanzapine Low - quetiapine	Not covered.	<p>Five trials of olanzapine were found; three reporting Body Mass Index (BMI) could be pooled. There was no difference in change in BMI at either one or three months compared with placebo.</p> <p>One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.</p>	Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.
Insomnia	Very low.	Not covered.	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be inefficacious in treating insomnia.

Table B. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Substance abuse – alcohol	Moderate – aripiprazole Low – quetiapine	Not covered.	Two trials of aripiprazole and one of quetiapine reported % of patients completely abstinent during follow-up. In our pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is inefficacious in treating alcohol abuse /dependence. Quetiapine may also be inefficacious .
Substance abuse – cocaine	Low	Not covered.	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is inefficacious in treating cocaine abuse /dependence. Risperidone may also be inefficacious .
Substance abuse – methamphetamine	Low	Not covered.	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is inefficacious in treating methamphetamine abuse/dependence.
Substance abuse – methadone clients	Low	Not covered.	One trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an inefficacious adjunct to methadone maintenance.

ADHD = attention-deficit hyperactivity disorder; BEHAVE-AD = Behavioral Pathology in Alzheimer’s Disease Scale; BPRS = Brief Psychiatric Rating Scale; CGI-BPD = Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I = Clinical Global Impression Improvement; CGI-S = Clinical Global Impression-Severity; CMAI = Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NPI = Neuropsychiatric Inventory; OCD = obsessive-compulsive disorder; PANSS = Positive and Negative Syndrome Scale; PCT = placebo-controlled trial; PTSD = post-traumatic stress disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitors; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder

Key Question 3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals. Only one study conducted a subgroup analysis by gender; there were no studies that stratified by racial or ethnic group. Although many studies specified age in their inclusion criteria, few studies stratified results by age.

Examination of the literature for differing efficacy of atypicals by clinical subsets did not reveal studies reporting subgroup analyses. Our own meta-analysis found efficacy for combat-related PTSD in men but not for PTSD in civilian women, although these data come from separate literatures, and head-to-head comparison of gender effects within study have not been performed. Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any other condition.

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Table C compares the most important findings regarding adverse events, by age group and study design.

Table C. Summary update: safety of atypical antipsychotics for off-label use

Adverse Event	Head-to-Head Comparisons	Active Comparisons	Placebo Comparisons
Weight gain – Elderly patients	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone than placebo according to our meta-analysis.
Weight gain – Adults 18–64	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Weight gain – Children & adolescents	No head-to-head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality – Elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we cannot make conclusions regarding safety here.

Table C. Summary update: safety of atypical antipsychotics for off-label use (continued)

Adverse Event	Head-to-Head Comparisons	Active Comparisons	Placebo Comparisons
Endocrine/ diabetes – Elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Endocrine/ diabetes – Adults 18–64	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA – Elderly patients	No evidence reported.	Hospitalization for CVA was increased in the first week after initiation of conventional antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.

Table C. Summary update: safety of atypical antipsychotics for off-label use (continued)

Adverse Event	Head-to-Head Comparisons	Active Comparisons	Placebo Comparisons
EPS – Elderly patients	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported.	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
EPS – Adults 18–64	No evidence reported.	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to our meta-analysis.
Sedation – Elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant.	No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials of olanzapine and three of risperidone versus conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Sedation – Children and adolescents	No head-to-head trials.	No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.
Sedation – Adults 18–64	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone versus olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in our pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in our meta-analysis.

BMI = body mass index; CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease; CVA = cerebrovascular accident; EPS = extrapyramidal symptoms; PCT = placebo-controlled trial; SSRI = serotonin selective reuptake inhibitor

Key Question 5. What is the effective dose and time limit for off-label indications?

There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed. Most trials used flexible dosing, resulting in patients taking a wide range of doses. According to a meta-analysis we were able to conduct using the percentage of remitters and responders according to the MADRS as outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs. More trials examining different doses of other atypicals for MDD would help guide clinicians in treating this population. In addition, more dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder would allow for pooling and comparison of results.

Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported followup time.

Remaining Issues

The overarching finding of this review is that although atypical antipsychotic medications are used for a large number of off-label indications, there is moderate to strong evidence of efficacy for only a few of the drugs and for only a few of the off-label indications. Most of the evidence is for the drugs risperidone, olanzapine, and quetiapine, for the off-label indications of dementia, depression, and OCD. For the newly approved atypicals (asenapine, iloperidone, and paliperidone), we found no clinical trials assessing their use for any off-label condition, and for some off-label uses, we found no or only a small number of trials. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label use suggests that efficacy differs between drugs, meaning that the assumption of a “class effect” for atypical antipsychotics may be unwarranted. This means that each drug requires its own evaluation of efficacy for each off-label indication, which is a large task; drugs demonstrated to be efficacious will need to be compared in head-to-head in trials.

There is almost no evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or medical comorbidities. In addition, existing evidence about the role of baseline severity of disease is too heterogeneous to allow us to draw conclusions. In future research, standardized measures of disease severity might allow for greater knowledge of the patient populations who would benefit from treatment with atypical agents.

Regarding adverse effects of the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event. It would facilitate assessments of comparative effectiveness if future studies contained a standardized list of assessed side effects. As many trials report only those side effects observed, we are unable to compare between trials for many of the side effects.

Another area where clinical guidance is needed is in the dosages required to achieve effects in off-label indications. The dosages used in off-label indications varied from those used in on-label indications. There were few trials that compared effects by dose. Most studies used “flexible” dosing, where a patient's dosage can be adjusted during the trial. Thus, a dosage comparison across trials was generally not possible. More research, examining differing dosages within the same population, is required in order to guide clinicians in the appropriate doses to prescribe. A similar issue is that of treatment length. More research reporting responses at various time points would be helpful in determining how long treatment is required. Given the

risk of side effects when using these agents, clinicians need to know when a result is expected to prevent continuing an inefficacious agent, unnecessarily.

Newer agents, such as asenapine, iloperidone, and paliperidone, cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence to date does not support that there is a general “class effect” in terms of either efficacy or harm for most off-label indications. Trials assessing the newer agents’ efficacy and safety are necessary if they are to be used off-label for any of the above treatment areas.

Introduction

Background

Antipsychotics medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These medications are commonly divided into two classes, reflecting two waves of historical development: the conventional antipsychotics and the atypical. The conventional antipsychotics served as the first successful pharmacologic treatment for primary psychotic disorders such as schizophrenia. Having been widely used for decades, the conventional antipsychotics also produced various side effects requiring additional medications, which spurred the development of the atypical antipsychotics.

Currently, nine atypical antipsychotic drugs have been approved by FDA: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. These drugs (except for the three recently approved ones—asenapine, iloperidone, and paliperidone) have been studied for off-label use in several conditions. A 2006 study¹ on Efficacy and Comparative Effectiveness of Off-label Use of Atypical Antipsychotics reviewed the scientific evidence on the safety, efficacy, and effectiveness for off-label uses. Clozapine was excluded because of its association with a potentially fatal blood disorder of bone marrow suppression and requires frequent blood tests for safety monitoring. Rarely used, except for treatment of schizophrenia, the drug has proven refractory to other treatment. The 2006 study examined 84 published studies on atypical antipsychotics and found that the most common off-label uses of the drugs were treatment of depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. It concluded that with few exceptions, there was insufficient high-quality evidence overall to reach conclusions about the efficacy of any off-label indications of these medications. It also found strong evidence that atypical antipsychotics can increase chances of adverse events such as significant weight gain, sedation, and gastrointestinal problems. Future research areas suggested by the study include safe treatment for agitation in dementia, association between the increased risk of death and antipsychotics drugs, and comparison of the development of adverse effects between patients taking atypical antipsychotics and those taking conventional antipsychotics.

Since publication of that report, important changes have occurred that could make it out of date. Studies have been published on new off-label uses, such as treatment of eating disorders, insomnia, attention-deficit hyperactivity disorder (ADHD), anxiety, and substance abuse. New or increased adverse effects of off-label indications have been observed and new atypicals (asenapine, iloperidone, and paliperidone) have been approved by FDA for the treatment of schizophrenia and bipolar disorder. In addition, the following previously off-label uses have been approved for on-label use by FDA:

- Quetiapine and quetiapine ER (extended release) as monotherapy in bipolar depression
- Quetiapine ER as augmentation for major depressive disorder (MDD)
- Aripiprazole as augmentation for MDD
- Olanzapine/fluoxetine combination for MDD
- Olanzapine/fluoxetine combination for bipolar depression
- Risperidone and aripiprazole for autism spectrum disorders.

An update is clearly needed to better understand the trend of off-label use and the risks and benefits associated with off-label use. Further, a number of issues remain unclear due to insufficient information in the previous report: subpopulations (i.e., race/ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. This update will try to address these issues.

Off-Label Conditions

The present study covers the following off-label uses of atypical antipsychotic medications: anxiety, ADHD, dementia and severe geriatric agitation, depression, eating disorder, insomnia, OCD, post-traumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome. Autism (included in the original systematic review) will be reviewed in a study on the comparative effectiveness of typical and atypical antipsychotics for on-label indications, conducted by another EPC.

Anxiety. Anxiety disorders include a number of disorders where the primary feature is abnormal or pathological fear and anxiety. Major types of disorders in this category include acute stress disorder, agoraphobia (with or without a history of panic disorder), generalized anxiety disorder (GAD), OCD, panic disorder (with or without agoraphobia), specific and PTSD. We will report OCD and PTSD separately.

While anxiety is a normal reaction to stress, when it becomes an excessive, irrational dread of everyday situations, it is considered a disabling disorder.² About 40 million American adults age 18 years and older (about 18 percent) suffer from anxiety disorders in a given year.³ Anxiety disorders can be treated with medication (e.g., antidepressants such as selective serotonin reuptake inhibitors or SSRIs, tricyclics), specific types of psychotherapy, or both.⁴

The most common anxiety disorder treated with atypicals is GAD. GAD is characterized by at least 6 months' persistent and excessive anxiety and worry. People with GAD cannot relax, cannot control the worry, startle easily, can be irritable, and have difficulty concentrating. GAD affects about 6.8 million American adults;³ and more women suffer from GAD than men.

Attention-Deficit Hyperactivity Disorder (ADHD). ADHD or AD/HD is a neurobehavioral developmental disorder. The Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition, text revision (DSM-IV-TR) recognizes three major subtypes of ADHD: predominantly inattentive subtype, predominantly hyperactive-impulsive subtype, and combined inattentive/hyperactive-impulsive subtype. Inattention, hyperactivity, and impulsivity are the key features of ADHD. To be diagnosed, one must have six (or more) of the inattention symptoms or six (or more) of the hyperactivity-impulsivity symptoms that have persisted for at least 6 months; some impairment from the symptoms must be present in at least two settings (e.g., at home and at school/work); some symptoms that cause impairment must be present before age 7; the symptoms must be severe enough to be considered maladaptive, be inconsistent with the patient's level of development, and not be exclusively due to another condition.

Treatments for ADHD include medication, psychotherapy, educational interventions, or a combination of treatments. While ADHD is the most common disorder diagnosed in school-age children, it can continue through adolescence and adulthood, and is no longer considered only a childhood disorder.

Dementia and Severe Geriatric Agitation. Dementia is a disorder of acquired deficits in more than one domain of cognitive functioning. These domains are memory, language production and understanding, naming and recognition, skilled motor activity, and planning and executive functioning. The most common dementias—Alzheimer’s and vascular dementia—are distinguished by their cause. Alzheimer’s dementia occurs with an insidious onset and continues on a degenerative course to death after 8 to 10 years;⁵ the intervening years are marked by significant disturbances of cognitive functioning and behavior, with severe debilitation in the ability to provide self-care. Vascular dementia refers to deficits of cognitive functioning that occur following either a cerebrovascular event—a stroke—leading to a macrovascular dementia, or, alternatively, more diffusely located changes in the smaller blood vessels, leading to a microvascular dementia. These (and other) dementia types commonly co-occur. Psychotic symptoms are frequent among dementia patients and include auditory hallucinations, believing that one’s personal belongings have been stolen, or believing that unknown others are cohabiting with the patient (phantom boarders). Although the cognitive deficits can be severe, it is the behavioral disturbances (such as yelling or combativeness with caregivers) that typically interfere with independent living and necessitate placement in a nursing home.

Management of dementia patients includes both behavioral and psychopharmacologic interventions.⁶ Although behavioral interventions are commonly used with dementia patients, they require the presence of trained caregivers. Psychopharmacologic treatments developed specifically for dementia include acetylcholinesterase inhibitors, which attempt to compensate for the loss of neurons that produce the neurotransmitter acetylcholine by inhibiting the enzyme responsible for its degradation. Antipsychotics, including the atypicals, have been used to control both psychotic symptoms and severe behavioral agitation in dementia.

Depression. Depression refers to a potentially severe episodic disturbance of mood, with a constellation of low mood, inability to experience pleasure, sleep and appetite disturbances, loss of energy, difficulty concentrating, thoughts of guilt, worthlessness, and hopelessness, and suicidal ideation.⁷ Depression is best thought of as a symptom cluster that can appear in several different psychiatric disorders. These disorders are unipolar depression, bipolar depression, major depression with psychotic features, and depression occurring during psychotic disorders, such as schizophrenia or schizoaffective disorder. (Full descriptions of the diagnostic criteria for these disorders and others discussed in this report can be found in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders, the DSM-IV-TR.)⁸

Unipolar depression refers to major depressive disorder and is defined by episodes of at least a majority of the above symptoms lasting at least two weeks. A particularly severe form of major depressive disorder occurs when the depression is accompanied by psychotic symptoms such as auditory hallucinations. Current treatment guidelines for the pharmacologic treatment of major depression are expressed algorithmically as a flowchart, with later steps tried after the failure of the earlier steps.⁹ Failure may occur for a variety of reasons, including intolerable side effects or lack of improvement after treatment of an appropriate duration. The mainstays of treatment are the antidepressants, including the serotonin reuptake inhibitors (SRIs), including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; the tricyclic antidepressants, including amitriptyline, imipramine, nortriptyline, and desipramine; and other drugs with dual reuptake inhibition or other mechanisms, including bupropion, duloxetine, mirtazapine, and venlafaxine. Other treatments used include augmenting agents, medications that are not themselves antidepressants, but that speed or improve the antidepressant activity; various psychotherapies;

and electroconvulsive therapy. Because of their serotonergic effects, the atypical antipsychotics have been tested as augmenting agents. For depression with psychotic features, the recommended psychopharmacologic treatment, which consists of the simultaneous use of antidepressants and antipsychotics—most often atypical antipsychotics has been advocated.^{9,10}

Eating Disorders. Eating disorders are a group of conditions characterized by severe disturbances in eating behavior. Disorders in this category include anorexia nervosa (refusing to maintain a minimally normal body weight) and bulimia nervosa (recurrent binge eating followed by compensatory behaviors such as self-induced vomiting).

DSM-IV-TR criteria⁸ for anorexia nervosa include a refusal to maintain body weight at or above a minimally normal weight for age and height, intense fear of gaining weight, three consecutive missed periods, and either refusal to admit the seriousness of the weight loss, or undue influence of shape or weight on one's self image, or a disturbed experience in one's shape or weight. Criteria for bulimia nervosa include recurrent binge eating and inappropriate compensatory behavior in order to prevent weight gain at least twice a week for 3 months, and self-evaluation unduly influenced by body shape and weight.

Causes of eating disorders are poorly understood. Eating disorders usually begin in late adolescence or early adult life, and affect both men and women, although women and girls are much more likely than men and boys to develop an eating disorder.¹¹ Eating disorders are treatable with medications, nutritional counseling, and psychotherapy.¹¹

Insomnia. Insomnia is one type of sleep disorder, characterized by persistent difficulty falling asleep and/or difficulty staying asleep. DSM-IV-TR⁸ organizes the sleep disorders into four major sections (primary sleep disorders, sleep disorder related to another mental disorder, sleep disorder due to a general medical condition, and substance-induced sleep disorder). This review defines insomnia broadly and covers all of the four types.

Causes of insomnia are various, including medications, pain from any injury, hormone shifts, mental disorders, restless legs syndrome, poor sleep hygiene (e.g., noise), medical conditions (e.g., hyperthyroidism), etc.¹² Criteria for a diagnosis of primary insomnia include: difficulty initiating or maintaining sleep, or nonrestorative sleep for at least one month; the disturbance must cause significant distress or impairment in social, occupational, or other important functions; the disturbance does not occur exclusively during the course of another mental or medical disorder and is not due to the direct physiological effects of alcohol, medication, or other substances.⁸

Obsessive-Compulsive Disorder (OCD). The essential features of OCD are obsessions (repetitive, intrusive, unwanted thoughts, impulses, or images) and compensatory compulsive behaviors that reduce or remove the distress caused by the obsessions. A common example would involve obsessions about fears of contamination by dirt or germs, which give rise to compulsions to wash one's hands excessively.¹³ The distress caused by the obsessions, and the time devoted to, or the dysfunction caused by, the compulsions can lead to serious psychiatric morbidity. Standard treatments include psychopharmacologic approaches using SRIs, such as fluoxetine, and cognitive-behavioral therapy, which promotes a kind of learning through exposure to the feared or unpleasant stimulus and prevention of the compulsive response. Limited response to both treatments is common, and various psychopharmacologic agents, including the atypical antipsychotics, have been tested for their ability to augment SRIs.

Post-traumatic Stress Disorder (PTSD). PTSD describes the development of characteristic disabling symptoms following exposure to trauma such as war or rape. These symptoms are grouped into three clusters: re-experiencing (nightmares, flashbacks), avoidance and numbing (avoidance of reminders of the trauma, inability to recall the trauma, feelings of detachment, restriction of emotion), and increased arousal (anger, problems with concentration, hypervigilance, exaggerated startle response).¹⁴ The symptoms of PTSD span diverse psychiatric categories, and include mood, anxiety, and psychotic symptoms (including auditory hallucinations, suspicion, dissociation, and emotional withdrawal). Treatment of PTSD involves medications that address each of these classes of symptoms (including atypical antipsychotics) and cognitive-behavioral and other psychotherapies.

Personality Disorders. A personality disorder is “an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual’s culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment.”⁸ The DSM-IV-TR defines 10 such disorders. Optimal treatment of such disorders is not well understood, although some of the disorders are the focus of active research. Because of the long-term nature of the disorders, they are often treated through psychotherapy in an attempt to facilitate long-term personality change, while psychiatric medications are thought to play a role in moderating some of the symptomatic manifestations. Only two personality disorders have been treated in clinical trials with atypical antipsychotics: schizotypal personality disorder (SPD) and borderline personality disorder (BPD).

SPD is defined by pervasive deficits in interpersonal relationships, cognitive and perceptual disturbances, and eccentric behavior. The perceptual and behavioral changes often appear similar to a mild form of schizophrenia, and there is some evidence of familial aggregation of SPD in relatives of those with schizophrenia.¹⁵ Because of this connection, treatment with atypical antipsychotics has been tried.

BPD’s essential characteristic is instability in interpersonal relationships, self-image, and mood, along with impulsive behavior, intense anger, and recurrent suicidal gestures or attempts. There are often severe dissociative symptoms and paranoid ideation, which may occur or worsen with stress. BPD is a significant cause of psychiatric morbidity, and, because of the increased risk for suicide, mortality. Effective treatment of BPD is an area of active research. The cornerstone of treatment is psychotherapy of various kinds, with dialectical behavior therapy and mentalization-based therapy, among others, having shown some efficacy in clinical trials.¹⁶ Psychiatric medications are also commonly used, to treat both comorbid conditions, such as mood disorders, and the symptoms of BPD, although the evidence supporting such use is not strong. Because of the occurrence of psychotic symptoms, and because atypical antipsychotics have mood stabilizing properties, they have been tried in the treatment of BPD.

Substance Abuse. The present report covers the substance-use disorders (abuse and dependence). Substances reviewed in this report include alcohol, cocaine, marijuana, heroin, ecstasy, methamphetamine, and opioids. Caffeine or nicotine dependence is not included in the current review.

When the individual continues use of the substance despite significant problems related to the substance, substance dependence may be diagnosed. According to DSM-IV-TR,⁸ to be diagnosed as substance dependence, three (or more) of the following must be present within a

12-month period: (1) tolerance; (2) withdrawal; (3) the substance is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects; (6) important social, occupational, or recreational activities are given up or reduced because of substance use; and (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem.

Substance abuse is a pattern of substance use leading to many adverse results from continual use. According to DSM-IV-TR,⁸ substance abuse involves one (or more) of the following within a 12-month period: (1) recurrent use resulting in a failure to fulfill major obligations at work, school, or home; (2) recurrent use in situations which are physically hazardous (e.g., driving while intoxicated); (3) legal problems resulting from recurrent use; or (4) continued use despite significant social or interpersonal problems caused by the substance use.

Tourette's Syndrome. Tourette's disorder refers to the condition of multiple motor and vocal tics, which are rapid, recurrent, stereotyped movements. Tics of Tourette's include eye blinking, facial grimacing, throat clearing, grunting, and, uncommonly, although most notably, coprolalia, the uttering of obscenities. The tics typically start around age 6 (the diagnosis requires that tics must appear by age 18). Pharmacologic treatments that have been tried include antipsychotic medications and medications from other classes, including clonidine, some of the tricyclic antidepressants, and benzodiazepines.

Scope and Key Questions

Key Questions

Key Question 1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question 2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

Sub-Key Question 2. How do atypical antipsychotic medications compare with other drugs, including conventional antipsychotics, for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses? Do efficacy, effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Demographic subsets include different racial/ethnic groups, different age groups, and both genders. For clinical subsets, it is expected that only a small number of trials investigate specific subtypes (for example, inattentive vs. hyperactive-impulsive type ADHD) which makes a comparative study infeasible. When data are available, clinical subtypes of the conditions of interest will be examined (for instance, combat-related PTSD and non-combat-related PTSD). Severity subsets of population are categorized as groups with mild, moderate, or severe condition.

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question 5. What is the effective dose and time limit for off-label indications?

Scope

Study populations covered by the present review are adults, defined as being at least 18 years of age, with the following disorders: OCD, PTSD, personality disorders (primarily borderline), agitation in dementia (primarily in the elderly), anxiety, and major depressive disorder. The following disorders are also studied among children (younger than 12 years old) and adolescents (12 to 17 years old): eating disorders (including anorexia nervosa and bulimia), ADHD, Tourette's syndrome, and insomnia.

Interventions are the following atypical antipsychotics approved by FDA: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, asenapine, and iloperidone. We included aripiprazole, olanzapine and quetiapine for depression, although these now are FDA approved for this indication, in order to provide readers with any potential direct or indirect evidence about comparative effectiveness with other atypical antipsychotics.

Four types of trials will be classified and examined:

1. "Head-to-head" trials: trials that compare one atypical antipsychotic to another and provide direct evidence of comparative efficacy;
2. "Active" controlled trials: trials that compare an atypical antipsychotic with another class of medication, often conventional antipsychotics;
3. "Placebo" controlled trials: trials that compare atypical antipsychotics with a placebo; and
4. "Augmentation" trials: trials that compare an antipsychotic taken with another medication with the other medication alone.

It is possible for a trial to include comparisons of more than one type; for example, a trial comparing risperidone, olanzapine, haloperidol, and placebo would include head-to-head, active, and placebo comparisons.

We will report efficacy and where available, effectiveness outcomes. For efficacy, we will report commonly used objective outcomes such as symptom scores, response rates, laboratory data, and time to disease recurrence; where effectiveness studies are available, we will report these outcomes plus general health outcomes (e.g., the SF-36) and quality of life.

All reported side effects and adverse events will be abstracted from clinical trials and large observational studies, regardless of study duration. The primary focus will be on the following adverse events: mortality, cardiovascular events (myocardial infarction, arrhythmia–tachycardia, and blood pressure increase/decrease), neurological events (cerebrovascular accident, akathisia, extrapyramidal symptoms, tardive dyskinesia, sedation, and dizziness), and metabolic disorders (weight gain/loss, hyperglycemia/diabetes, and hyperlipidemia).

Methods

Topic Development

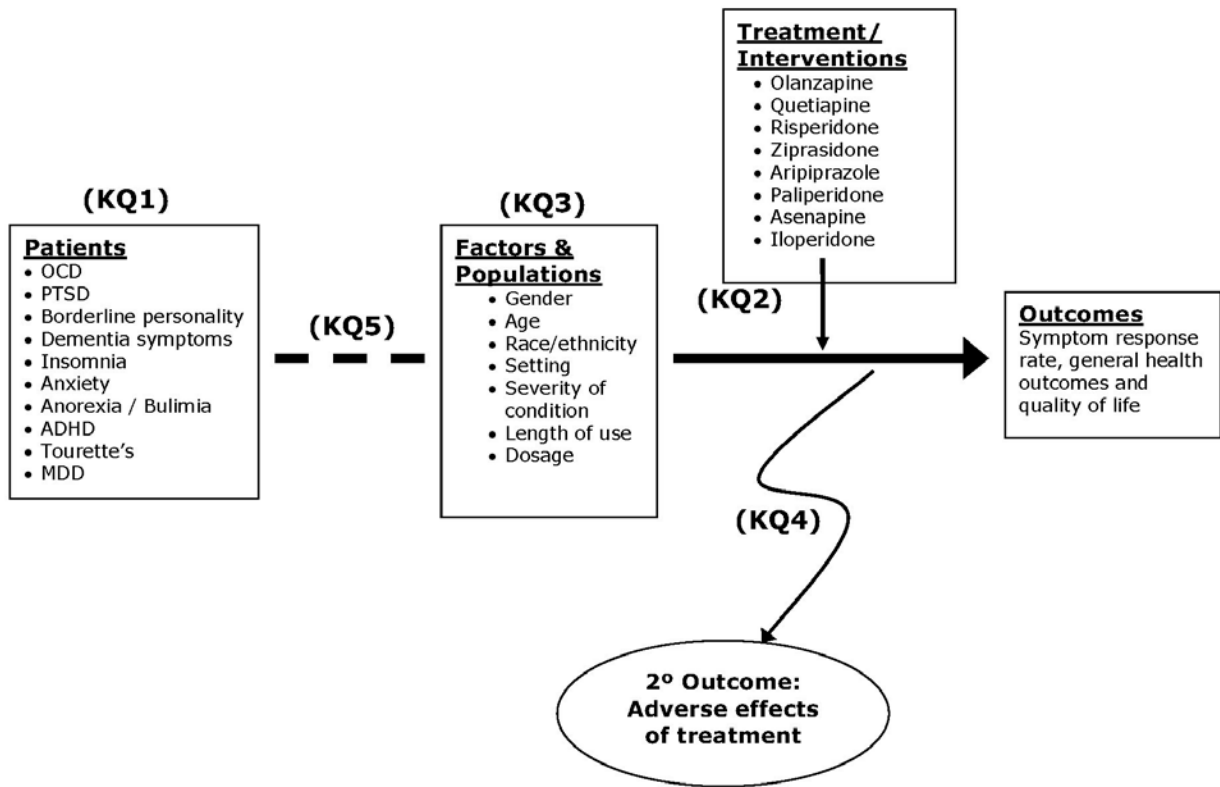
The current report is designed to update Efficacy and Comparative Effectiveness of Atypical Antipsychotics for Off-label Use, which the Agency for Healthcare Research and Quality (AHRQ) published in 2006. Since this is an update, we tried to be as consistent as possible with regard to the general topics, scope of work, and analytical methods, but made revisions to reflect the important changes mentioned in the introduction. The key questions were posted on the AHRQ Effective Health Care Program Web site to obtain public comments which were considered when focusing the scope of this report. The present evidence report focuses on eight Food and Drug Administration (FDA)-approved atypical antipsychotics (clozapine was excluded because of its documented severe or life-threatening side effects) used for the following psychiatric conditions: anxiety, attention-deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, depression, eating disorder, insomnia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome. We reviewed all conditions among adults (defined as 18 years old and older); for ADHD, eating disorders, insomnia, and Tourette's syndrome, children (younger than 12 years old) and adolescents (12–17 years old) were also included. Autism, which was included in the original study, is included in a report on the comparative effectiveness of typical and atypical antipsychotics for on-label indications conducted by another Evidence-based Practice Center. Thus, autism is excluded from the present review.

Analytic Framework

Figure 1 presents the analytic framework for the update of this Comparative Effectiveness Review, with the five Key Questions depicted. First, by reviewing utilization data, surveys on prescribing patterns, and general information about the leading off-label uses, new off-label uses and trends in utilization in the target populations are summarized. Next, by using data from clinical trials and large cohort studies, evidence of benefits and harms in treating the mental health conditions is documented. The evidence of benefits—efficacy and comparative effectiveness (vs. placebo, vs. other atypicals, or vs. conventional therapy) for the off-label indications—is evaluated separately for each of the atypical antipsychotics within condition (dementia, OCD, PTSD, depression, etc.) via the examination of selected outcome measures, mainly symptom response rates measured by recognized psychometric tools.

Benefits and harms for specific subpopulations (by gender, age, and race/ethnicity) or related to other important factors (setting, severity of condition, length of use, and dosage) are documented. Special attention is given to identify the efficacious dose and time limit for off-label indications. The evidence of risks—adverse events associated with off-label indications—is summarized, first within individual drugs across condition, and then compared within the class and with other drugs used for the conditions.

Figure 1. Analytic framework for comparative effectiveness review: off-label uses of atypical antipsychotics



Search Strategy

We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011. Searches for utilization data were conducted, as were searches for use for new conditions (anxiety, ADHD, eating disorders, insomnia, and substance abuse). Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO. A summary of detailed search strategies is available in Appendix A. Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases.

Technical Expert Panel

A Technical Expert Panel (TEP) provided expertise and different perspectives on the topic of this review. We invited a distinguished group of scientists and clinicians to participate in the TEP. We aimed to have at least one expert on each psychiatric condition on our TEP. TEP conference calls were held in November 2009 and February 2010. TEP members and their affiliations are listed in the front matter.

The TEP provided valuable information throughout the entire study. It provided information to identify literature search strategies; helped to decide appropriate outcome measures for specific psychiatric conditions and to identify recently published or ongoing clinical trials; and recommended approaches to specific issues raised from the public posting.

Study Selection

Two trained researchers reviewed the list of titles resulting from our electronic searches and selected articles to obtain. Each article retrieved was reviewed with a brief screening form (see Appendix B: screener) that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration. Clinical trials were used to review efficacy outcomes. In the case that no clinical trials were found for a given condition or drug of interest, we turned to observational studies.

All reported side effects and adverse events were abstracted from clinical trials, even if the trial did not report efficacy or effectiveness results. We also included large observational studies of adverse events. Reports of utilization and prescribing patterns were accepted if they discussed use in the United States since 1995.

Data Extraction

Data were independently abstracted by a health services researcher and a psychiatrist trained in the critical assessment of evidence. The following data were abstracted from included trials: trial name, setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, interventions (dose, frequency, and duration), any co-interventions, other allowed medication, comparisons, and results for each outcome. Data abstraction forms are provided in Appendix B.

For efficacy and effectiveness outcomes, a statistician extracted data. Published summary data for each treatment or placebo arm within a trial was collected. For outcomes that reported count data, event counts and sample sizes by group were extracted. For continuous outcomes, sample size, mean difference and standard deviations were extracted. If a study did not report a mean difference by outcome or if a mean difference could not be calculated from the given data, the study was excluded from analysis. For those trials that did not report a followup standard deviation, we imputed one by assigning the weighted mean standard deviation from other trials that reported the standard deviation for the same outcome.

Data from publications reporting adverse events were extracted by two reviewers and reconciled by a third. Since the most common type of data reported across adverse event publications were sample size and number of people with each event, we collected this

information by treatment. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. A trial needed to report at least instance of an adverse event in order to be included in the analysis of that adverse event. This decision may over- or underestimate the number of patients with that adverse event, but seems the only logical choice.

Quality Assessment

To assess internal validity, we abstracted data on the adequacy of the randomization method; the adequacy of allocation concealment; maintenance of blinding; similarity of compared groups at baseline and the author's explanation of the effect of any between-group differences in important confounders or prognostic characteristics; specification of eligibility criteria; maintenance of comparable groups (i.e., reporting of dropouts, attrition, crossover, adherence, and contamination); the overall proportion of subjects lost to followup and important differences between treatments; use of intent-to-treat analysis; post-randomization exclusions, and source of funding. We defined loss to followup as the number of patients excluded from efficacy analyses, expressed as a proportion of the number of patients randomized.

To assess external validity, we recorded the number screened, eligible, and enrolled; the use of run-in and washout periods or highly selective criteria; the use of standard care in the control group; and overall relevance. Funding source was also abstracted.

To arrive at a quantitative measure, we used the Jadad scale, which was developed for drug trials. This method measures quality on a scale that ranges from 0 to 5, assigning points for randomization, blinding, and accounting for withdrawals and dropouts.¹⁷ Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared with trials scoring 3-5.¹⁸ The latter have been called "good" quality and the former called "poor" quality.

The Newcastle-Ottawa Scale¹⁹ was used to assess internal validity of observational studies of adverse events.

Applicability

People may use "efficacy" and "effectiveness" of an intervention interchangeably, but they have important differences. CERs assess internal validity and external validity (e.g., applicability or generalizability) of included studies. Internal validity is emphasized in efficacy studies, while applicability is emphasized in effectiveness studies. The efficacy of an intervention measures the extent to which the intervention works under ideal circumstances, and the effectiveness of an intervention measures the extent to which the intervention works under real world conditions.²⁰ Therefore, designs of effectiveness trials are based on conditions of routine clinical practice, and outcomes of effectiveness trials are more essential for real world clinical decisions.

The fundamental distinction between efficacy and effectiveness studies lies in the populations and control over the intervention(s).²¹ Efficacy studies tend to be performed on referred patients and in specialty settings, and enrolled populations are highly selected (patients with comorbidities may be excluded); effectiveness studies are usually conducted on populations in primary care settings, which reflect the heterogeneity of the general population and thus are more representative. The vast majority of studies included in our report are efficacy studies as there are few effectiveness studies reporting health outcomes of interest. However, effectiveness studies are included in our analyses of adverse events.

Rating the Body of Evidence

We assessed the overall strength of evidence for intervention efficacy using guidance suggested by AHRQ for its Effective Health Care Program.²² This method is based loosely on one developed by the Grade Working Group,²³ and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. A brief description of the required domains is displayed in Table 1 below. For this report, we used both this scoring scheme and the global implicit judgment about “confidence” in the result. Where the two disagreed, we went with the lower classification.

Table 1. Grading the strength of a body of evidence: required domains and their definitions

Domain	Definition and Elements	Score and Application
Risk of Bias	<p>Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements:</p> <ul style="list-style-type: none"> • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. <p>Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies</p>	<p>Use one of three levels of aggregate risk of bias:</p> <ul style="list-style-type: none"> • Low risk of bias • Medium risk of bias • High risk of bias
Consistency	<p>The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements:</p> <ul style="list-style-type: none"> • Effect sizes have the same sign (that is, are on the same side of “no effect”) • The range of effect sizes is narrow. 	<p>Use one of three levels of consistency:</p> <ul style="list-style-type: none"> • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) <p>As noted in the text, single-study evidence bases (even megatrials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”</p>
Directness	<p>The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes.</p> <p>Two types of directness, which can coexist, may be of concern: Evidence is indirect if:</p> <ul style="list-style-type: none"> • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B – that is, studies of A versus placebo and B versus placebo, or studies of A versus C and B versus C but not A versus B. <p>Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes.</p> <p>Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.</p>	<p>Score dichotomously as one of two levels directness</p> <ul style="list-style-type: none"> • Direct • Indirect <p>If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.</p>

Table 1. Grading the strength of a body of evidence: required domains and their definitions (continued)

Domain	Definition and Elements	Score and Application
Precision	<p>Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately)</p> <p>If a meta-analysis was performed, this will be the confidence interval around the summary effect size.</p>	<p>Score dichotomously as one of two levels of precision:</p> <ul style="list-style-type: none"> • Precise • Imprecise <p>A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.</p>

EPC = Evidence-based Practice Center

Data Synthesis

We constructed evidence tables displaying the study characteristics and results for all included trials (Appendix D). Trials that evaluated one atypical antipsychotic against another and provided direct evidence were classified as “head-to-head” trials. “Active” controlled trials compared an atypical antipsychotic with another class of medication. Trials that compared atypical antipsychotics with a placebo were referred to as “Placebo” controlled trials. Finally, trials that compared an antipsychotic taken with another medication with the other medication alone were examined (referred to as augmentation trials). We provided four separate evidence tables, one for each type of study (head-to-head, active control, placebo control, and augmentation).

Efficacy

For the efficacy analyses, we focused on controlled trials. Effect sizes were calculated for each comparison, for studies reporting a continuous outcome. If all trials within a condition and subgroup used the same scale, then the effect size did not need to be standardized and a mean difference was calculated. For subgroups where pooling was done across several scales, we calculated a standardized mean difference using the Hedges’ *g* effect size.²⁴ A positive effect size indicates that the atypical drug has a higher efficacy than does the comparison arm (active control or placebo arm). Effect sizes of 0.20 or smaller were considered small, sizes of 0.50 and greater were considered large, and those between were considered moderate.²⁵

For outcomes that reported count data (number of events), relative risks (RR) were calculated. An RR greater than one indicates that the atypical has higher efficacy than does the comparison arm.

Based on important outcomes suggested by the TEP, a psychiatrist chose which outcomes were most appropriate to pool. Poolability across studies was also important; the psychiatrist, the statistician, and the project team jointly made the selection based on their professional knowledge and also considering the frequency of an outcome measure being reported by the trials. A minimum of three studies was required for meta-analysis. An effect size or relative risk was calculated for studies that reported data but did not contribute to a pooled analysis.

For trials that were judged sufficiently clinically similar to warrant meta-analysis, we estimated a pooled random-effects estimate²⁶ of the overall effect size or RR in outcome measures. The individual trial outcomes were weighted by both within-study variation and between-study variation in this synthesis.

We assessed publication bias for each condition that is pooled. Tests were conducted using the Begg adjusted rank correlation test²⁷ and the Egger regression asymmetry test.²⁸ Heterogeneity was assessed using the Q test and I-squared²⁹ test. All meta-analyses were conducted with Stata statistical software, version 10.0 (Stata Corp., College Station, Texas).³⁰

We reviewed and when appropriate included studies used in the 2006 CER. For efficacy outcomes, pooled analysis included both new studies and those included in the 2006 CER when clinically similar.

Adverse Events

All adverse-event data from the prior report were combined with adverse event data extracted from new studies, as long as there was no overlap. We identified mutually exclusive groups of similar events, based on clinical expertise. For example, events that affected the head, ear, eye, nose, or throat were grouped together as HEENT. For each adverse-event group, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the treatment group as well as the number who were observed to have experienced the event. We then report the analogous counts for the control groups.

Adverse events were analyzed based on three comparison types: atypical antipsychotic versus placebo; atypical antipsychotics versus other atypical antipsychotics, and atypical antipsychotics versus another active drug.

For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class. For our own analyses, we divided the study populations into three groups to make them more clinically homogeneous with respect to adverse events: children and adolescents, adults, and the elderly (i.e., the dementia trials).

For subgroups of events that occurred in two or more trials, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95 percent confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs v6.1 (Cytel Software, Cambridge, MA).

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with the atypical antipsychotic is larger than the odds associated with the comparison (placebo, active control, or other antipsychotic) group. We calculated number needed to harm (NNH) where this occurred. We note that if no events were observed in the comparison group, but events were observed in the intervention group, the odds ratio is infinity and the associated confidence interval is bounded only from below. In such a case, we report the lower bound of the confidence interval. If no events were observed in either group, the odds ratio is undefined, which we denote as “Not calculated (NC)” in the results tables.

Peer Review and Public Commentary

Experts on the various psychiatric conditions and various stakeholder communities (listed in the Acknowledgements section) performed an external peer review of this CER. The AHRQ Effective Health Care Program SRC located at Oregon Health Sciences University oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report and encouraged to suggest any relevant studies we may have missed. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. The SRC placed the draft report on the AHRQ Effective Health Care Program Web site (<http://effectivehealthcare.ahrq.gov/>) for public comment and compiled the comments for our review. We also requested review from each member of our TEP.

Results

In total, EPC reviewers selected 1,144 relevant titles for abstract review out of 9,414 titles. Electronic literature searches identified 9,207 titles, 216 were identified from reference mining, and 23 others not found in the electronic searches were included in Scientific Information Packets sent by drug manufacturers (Figure 2). Eighty-one were rejected through our abstract review, and 15 could not be obtained. Thus, 1,048 full-text articles/reports were available for short form screening.

Screening of retrieved articles resulted in further exclusion of 663. Reasons for exclusion include: no psychiatric condition of interest (i.e., not off-label conditions: 300 articles), study design (108 nonsystematic reviews, 60 case reports, 50 observational studies, 56 descriptive papers, and four other design), no drug/topic of interest (30 articles), foreign language (27 articles), no efficacy, effectiveness, safety, or utilization outcomes (6 articles), no human cases included (1 article), and 21 articles containing duplicate data, most of the duplicates were conference abstracts of studies that were later published as journal articles. We also identified 54 systematic reviews.

Among the 331 individual studies accepted based on short form review, there are 128 controlled trials (of which 122 reported efficacy outcomes) and 297 studies reporting adverse events (in our adverse event analysis, we focused on 129 studies which were either controlled trials or large observational studies). Eighteen articles contain information on utilization/prescription patterns in the United States.

The second page of Figure 2 displays the 122 new controlled trials that reported efficacy results along with 55 trials included in our 2006 Comparative Effectiveness Review (CER). Among these trials, seven reported duplicate data, and one had no comparison of interest; these were excluded. This left us 169 studies in total for our efficacy synthesis, with some studies contributing evidence to multiple conditions. The bottom of the second page of Figure 2 displays number of studies for each individual condition.

Figure 2. Literature flow

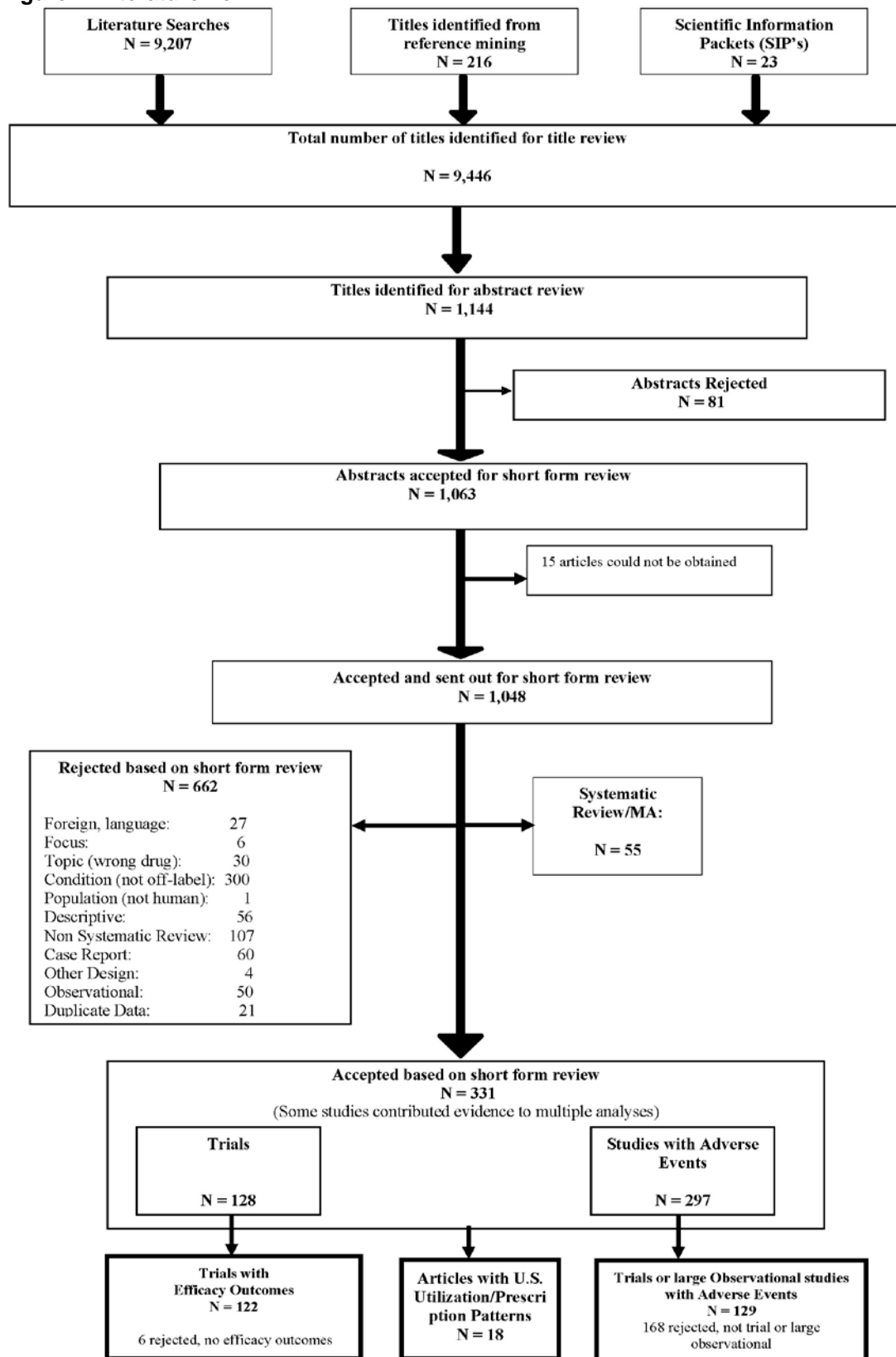
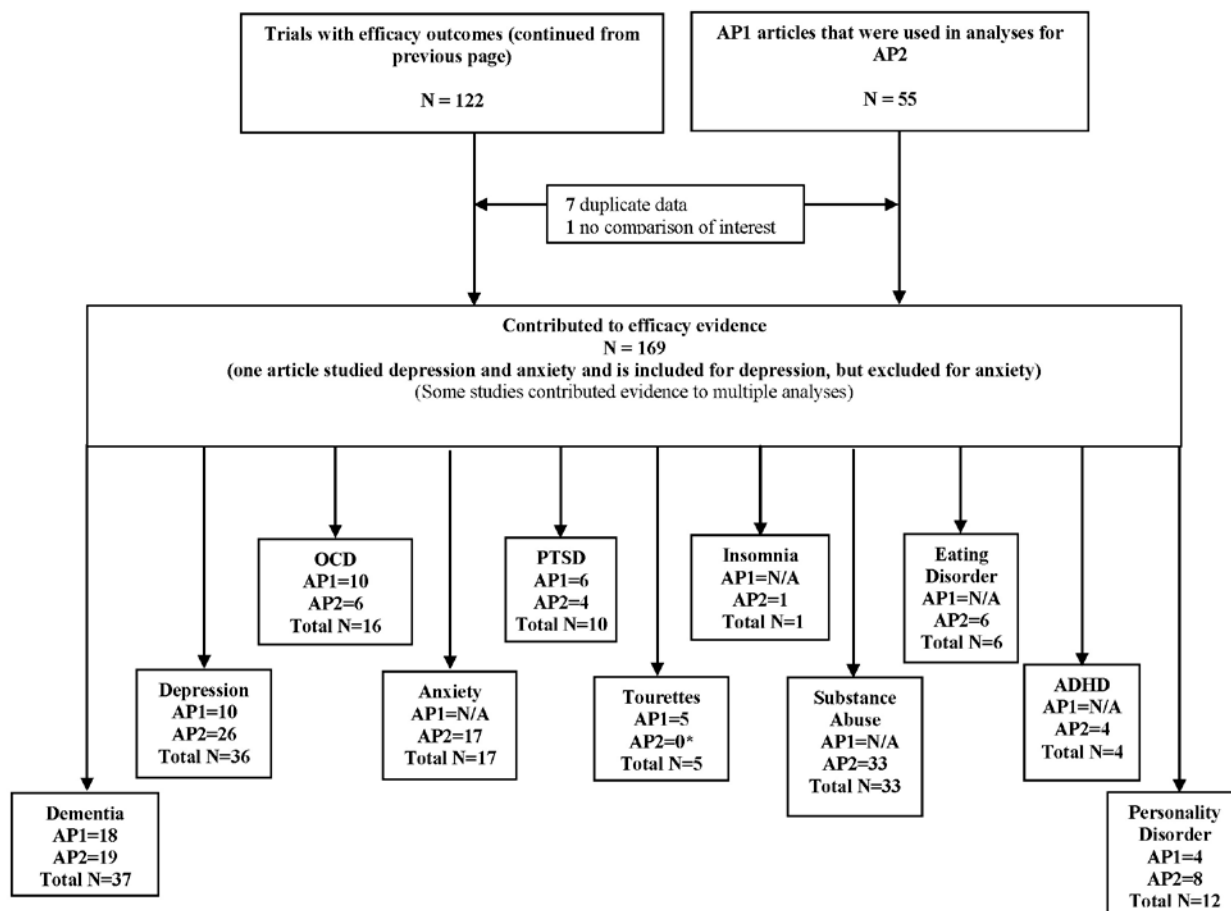


Figure 2. Literature flow (continued)



* Where trials did not exist, we described observational studies.
 AP1=Evidence Report 2006, AP2=Updated 2011 Evidence Report

Key Question 1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Points

Off-label use of atypical antipsychotics in various settings increased rapidly after their introduction in the 1990s.

Use of atypical antipsychotics for the following off-label conditions has been documented in the scientific literature: attention-deficit hyperactivity disorder (ADHD), anxiety, dementia in elderly patients, depression, eating disorders, insomnia, obsessive compulsive disorder, personality disorder, post-traumatic stress disorder (PTSD), substance use disorders, and Tourette’s syndrome.

Risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.

We found no reports describing off-label use of asenapine, iloperidone, and paliperidone.

According to a 2007 study, the use of atypical antipsychotics in the elderly is much higher in long-term care settings than in the community.

In 2004, nearly 25 percent of the elderly nursing home population received antipsychotics, with most receiving atypicals; males were more likely than females to receive them.

One year after the 2005 Food and Drug Administration (FDA) advisory warning, no state had actually changed its prior authorization policy in response to limit the use of atypicals in dementia. However, a more recent study concluded that the FDA advisory decreased the use of atypical antipsychotics in the U.S., especially among elderly dementia patients.

In 2003–2004, antipsychotics were prescribed in only 1 percent of overall mental health visits by children and adolescents, with most (99 percent) of these visits involving prescribing of atypicals.

Male children/adolescents were more likely than females to be prescribed atypical antipsychotics. Risperidone was the atypical most commonly prescribed to children.

At one large acute-care psychiatric hospital, quetiapine was used extensively for off-label conditions, and in a variety of off-label doses: only a quarter of patients had one of the diagnoses for which quetiapine is approved, and only a third received quetiapine in a standing dose regimen. Depression and substance-use disorders were found to be the most common associated diagnoses.

Atypicals are frequently prescribed to treat PTSD in the U.S. Department of Veterans Affairs (VA) health system.

Detailed Analysis

Overall utilization/prescription patterns in the United States. Our search identified 39 papers describing utilization/prescription patterns of antipsychotics (including atypical antipsychotics) in the United States. The majority examined conventional antipsychotics, atypical antipsychotics, and other agents simultaneously. Many of them investigated both on-label and off-label uses of atypicals. Table 2 presents information about settings, dates, sample size, drugs, conditions, and findings from large U.S. utilization studies with representative populations.

Reports have shown widespread off-label use of atypical antipsychotics in various settings since their introduction in the 1990s,³¹⁻³⁷ and such use has increased significantly in the past decade. The following conditions related to off-label use of atypical antipsychotics have been documented: ADHD, autism, anxiety, dementia, depression, eating disorders, insomnia, obsessive compulsive disorder, personality disorder, PTSD, substance-use disorders, and Tourette's syndrome. Risperidone, quetiapine, and olanzapine have been identified as the most commonly prescribed agents.

Utilization/prescription patterns among the elderly. Compared with other populations, use of atypical antipsychotics among the elderly has been given more attention, probably due to the widespread use of these drugs in dementia and Alzheimer's³⁸ and the fatal risk reported with this use. Studies have examined utilization patterns in both long-term care and in community settings in the United States.

Prescription of atypicals to treat dementia differs by gender and setting. One study³⁹ found that use of atypical antipsychotics—especially risperidone, olanzapine, and quetiapine—was

much higher in long-term care settings (21.0 percent, 11.9 percent, and 7.1 percent, respectively) than in the community (5.1 percent, 4.0 percent, and 2.3 percent, respectively). Another study⁴⁰ used the 2004 National Nursing Home Survey data and found widespread off-label use of antipsychotic drugs for conditions such as dementia, anxiety, and depression. Nearly 25 percent of the elderly nursing home population received antipsychotics, with most receiving atypicals. Males were more likely than females to receive atypicals. However, data from another nationally representative survey⁴¹ concluded that among community-dwelling elderly, gender was not significantly associated with atypical antipsychotics use. The authors also found significantly increasing use of atypicals among this population: after 1998, atypical use was more than 10 times as great as in 1996–1998. Elderly patients with poorer perceived mental health were more likely to receive atypicals rather than conventional antipsychotics. This is consistent with earlier findings.⁴⁰

When increasing evidence showed serious adverse events associated with the use of atypical antipsychotics among elderly people with dementia, regulatory warnings were issued. In both the United States and Canada, regulatory agencies (FDA and Health Canada) issued advisory warnings to health care professionals in 2005, describing increased mortality among elderly people with dementia who were taking atypical antipsychotics. Four studies examined the impact of these warnings. In the United States, Polinski⁴² found that more than one year after the FDA advisory warning, no state had actually changed its prior authorization policy in response to limit the use of atypicals in dementia. A more recent study⁴³ compared atypical antipsychotics use before and after the FDA advisory and concluded that the FDA advisory was associated with decreases in both on-label and off-label uses of atypical antipsychotics. The decrease was more rapid among elderly patients with dementia. In contrast, Saad and colleagues⁴⁴ conducted a survey of health care professionals and found that although most were aware of the FDA warning, only half (49 percent) reported that they changed the way of prescribing based on this notification. Reasons why they did not respond to the warning include: no alternative treatment available, lack of guidance, lack of evidence, and poor data availability. The authors concluded that antipsychotics continued to be prescribed for dementia among older adults. Finally, in Canada, Valiyeva⁴⁵ found that regulatory warnings were associated with small relative decrease (3 percent–5 percent) in the use of atypicals among elderly patients with dementia, but they did not reduce the overall prescription rate. Despite these decreases, atypical antipsychotics continued to be a common treatment option used among elderly dementia patients.

Utilization/prescription patterns among children and adolescents. Several studies examined prescription patterns of atypical antipsychotics among children and adolescents, indicating wide prescription and recent growth in the treatment of depression, anxiety, and other mental health problems.

Some studies discussed utilization in general, without focusing on off-label conditions. Olfson⁴⁶ examined national trends in the outpatient treatment of children and adolescents with antipsychotics from 1993 to 2002. Although not focusing on off-label uses of the drugs, they found that atypical antipsychotics were being widely prescribed to children and adolescents: a sharp increase was found from 2000 to 2002, when atypicals composed 92.3 percent of the antipsychotics prescribed in office-based practice. Aparasu⁴⁷ found that atypical antipsychotics were extensively prescribed to children and adolescents in 2003–2004: in total, antipsychotics were prescribed in 1 percent of overall visits by children and adolescents, with most (99 percent)

of these visits involving prescribing of atypicals. The most frequently used atypicals were risperidone, quetiapine, and aripiprazole; males and whites were more likely to these drugs.

Other studies provided details on specific conditions targeted. Cooper⁴⁸ conducted a cohort study to identify new use of antipsychotics among patients aged 2 to 18 years enrolled in Tennessee's managed care program for Medicaid enrollees and the uninsured (TennCare). They found that new users of antipsychotics nearly doubled from 1996 to 2001. The proportion of new users prescribed atypicals increased from 6.8 percent in 1996 to 95.9 percent in 2001. New use for ADHD increased 2.5-fold, while new use for Tourette's and autism remained stable. More recently, Pathak and colleagues⁴⁹ examined prescription trend of atypical antipsychotics among 11,700 Arkansas Medicaid-covered children under age 18 who were newly treated with atypical antipsychotics from 2001 through 2005. They found the number of children receiving the medications doubled during this period, increasing from 1,482 in 2001 to 3,110 in 2005; roughly 431 children each year initiated treatment with atypical antipsychotics. The most common condition was ADHD, followed by depression, conduct disorder, oppositional defiant disorder, and adjustment reactions. Most new users were given an initial prescription for risperidone. According to the authors, 41.3 percent of the new users had no diagnosis for which such treatment was supported by any published study, and 77.1 percent of aripiprazole use was not supported by any published evidence. Halloran and colleagues⁵⁰ examined prescription patterns of atypical antipsychotics among 172,766 privately insured children aged 2 to 18 in the United States between 2002 and 2005. Their findings also suggested a persistent trend in this population: the 1-year prevalence of atypical antipsychotics use increased from 7.9 (per 1,000) in 2002 to 8.1 in 2003, 8.6 in 2004, and 9.0 in 2005. The prevalence was generally lower in girls than boys, with boys almost two times as likely as girls to receive atypical antipsychotics. The most common condition was disruptive behavior disorder (67 percent), followed by mood disorders (65 percent), and anxiety disorder (43 percent). Risperidone (53 percent) was the most commonly prescribed atypical antipsychotic, followed by quetiapine (33 percent). A large proportion (75 percent) of children on these drugs had more than one psychiatric diagnosis during the study period.

Other relevant utilization findings. Seven papers⁵¹⁻⁵⁷ examined treatment of PTSD, mostly among VA populations; only one of them specifically focused on atypical antipsychotics. They documented that antipsychotics (including atypicals) have been frequently used in treatment of PTSD and comorbid disorders. One study⁵⁵ found that among a group of Medicaid recipients in New Hampshire atypical antipsychotics were more frequently prescribed when PTSD co-occurred with major depression.

A recent national study of VA records⁵⁷ indicates that quetiapine and risperidone were the atypicals most frequently prescribed off-label. PTSD was the most common off-label diagnosis, followed by "minor depression."

Philip⁵⁸ investigated 2-year trends of off-label prescribing practices of quetiapine at an acute-care psychiatric hospital. They found that quetiapine was used extensively for off-label conditions, and in a variety of off-label doses: only a quarter of patients had one of the diagnoses for which quetiapine is approved, and only a third received quetiapine in a standing dose regimen. Depression and substance use disorders were found to be the most common associated diagnoses.

Antipsychotic monotherapy (use of only one antipsychotic agent), concomitant therapy (simultaneous use of two or more antipsychotic agents), and combination of antipsychotics and

other agents have been studied.^{33,35,36,59} Their findings supported an increasing prevalence of atypical antipsychotics prescription.

Utilization/prescription patterns in other countries. Seventeen papers discussed utilization/prescription patterns of atypical antipsychotics in countries other than the United States: five in Canada, three in the United Kingdom, two each in France, Australia, and Turkey, and one each in Germany, New Zealand, and Italy. The studies documented widespread off-label uses of atypical antipsychotics in treating anxiety,⁶⁰⁻⁶⁴ ADHD,^{63,65} personality disorder,⁶⁴ depression,^{63,64,66} dementia,⁶⁷⁻⁷² eating disorders⁷³ and other conditions. Like in the United States, common off-label use of atypicals and significant increase in such use have been seen in other countries^{64,69,71,74} risperidone, quetiapine, and olanzapine were the most frequently used atypicals.^{61,63,69}

Table 2. Large utilization studies in the United States

Author/ Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
ADULTS								
Alexander, 2011 ³⁷	Outpatient	1995-2008	4,800 MDs	IMS Health National Disease and Therapeutic Index physician survey	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole, Paliperidone	On-label uses, depression, anxiety, ADHD, dementia	In 1995, 84% of antipsychotic visits involved conventional agents; by 2008 93% of visits involved atypicals. In 2008, 14% of atypicals were prescribed for depression.
Aparasu, 2005 ³³	Outpatient	2003 - 2004	2,860	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Depression, anxiety, dementia	Extensive concomitant antipsychotic therapy (simultaneous use of two or more antipsychotic agents) was found in outpatient settings. Risperidone, olanzapine, and quetiapine were commonly used in concomitant therapy and monotherapy.
Chen, 2006 ⁷⁵	All	2001	33,406	Claim data analysis	Georgia	Olanzapine, Quetiapine, Risperidone	All off-label conditions; not specified	The off-label use of antipsychotics is highly prevalent.
Dorsey, 2010 ⁴³	Physician Office	2003 - 2008	4,800	Drug prescribing data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole, Paliperidone	Dementia	The FDA Black Box advisory was associated with decrease in the use of atypical antipsychotics (fell 2% overall), especially among the elderly with dementia (fell 19%). Both on-label and off- label uses declined through 2008.
Gruber- Baldini, 2007 ³⁹	Nursing homes and community- dwelling	2002	12,697	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone	Dementia, Alzheimer's	Use of atypical antipsychotics, especially olanzapine, quetiapine, and risperidone, was much higher in long-term care settings than in the community.

Table 2. Large utilization studies in the United States (continued)

Author/ Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Jano, 2008 ⁴¹	Community -dwelling	1996 - 2004	32,737	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Anxiety, dementia	The most common diagnoses for antipsychotics use were dementia, anxiety, and schizophrenia; roughly the same proportion received typicals and atypicals; the most frequently used atypicals were risperidone, olanzapine, and quetiapine. After 1998, atypical use was over ten times more than in 1996 – 1998. Elderly patients with poorer perceived mental health were more likely to receive atypicals rather than typicals.
Kamble, 2008 ⁴⁰	Nursing homes	2004	11,939	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Dementia, depression, anxiety	Wide off-label use in conditions such as dementia, anxiety, depression was found among the elderly. Nearly 25% of nursing home elderly received antipsychotics, with most receiving atypicals. Males were more likely than females to receive atypicals.
Leslie, 2009 ⁵⁷	Veterans Administra tion	2007	279,778	Administrative Database	Nationally representative	Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone	Depression, anxiety, dementia, PTSD, substance abuse	60% of individuals who received an antipsychotic had no record of FDA- approved diagnosis. 79.5% of prescriptions were for atypicals (as opposed to conventional agents).
Morrato, 2007 ⁵⁹	All	1998 - 2003	55,481	Medicaid claim data analysis	Multistate	Olanzapine, Quetiapine, Risperidone	Depression, substance abuse	The mean prevalence of long-term antipsychotic polypharmacy in the year after initiating antipsychotics was 6.4%. Antipsychotic polypharmacy was more common in patients with more severe mental illness.

Table 2. Large utilization studies in the United States (continued)

Author/ Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Rosenheck, 2001 ⁵⁶	Veterans Administra- tion	1999	73,981	Chart review	Nationally representative	Olanzapine, Quetiapine, Risperidone	Depression, PTSD, Alzheimer's, dementia	Substantial off-label use of atypicals (42.8%) was evidenced, although a majority of patients were diagnosed with schizophrenia.
Sankaran- arayanan, 2007 ³⁶	Emergency department (ED)	2000 - 2004	2 million visits	Survey data analysis	Nationally representative	All; not specified	Depression, anxiety, substance use disorder	55% and 8% psychiatric ED visits involved atypical and typical-atypical combination prescriptions, respectively; there were 8-fold and 3.5-fold increase in ED visits with combination and atypical prescriptions, respectively. Patients with depression were more likely to receive atypical versus typical antipsychotics in the ED settings.
Sankaran- arayanan, 2007 ³⁵	Outpatient	1996 - 2003	356,885	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone	Depression, anxiety, dementia	From 1996/1997 to 2002/2003, visits involving atypical and combination antipsychotics saw large increases: 195% and 149%, respectively, while visits involving typicals decreased by 71%. More atypicals than typicals and combinations were used at US ambulatory care visits by patients with mental health disorders. Atypicals were less likely involved with visits by adults aged 41 to 64 years old and those with public insurance, but more likely by those with depression.

Table 2. Large utilization studies in the United States (continued)

Author/ Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
CHILDREN/ADOLESCENTS								
Aparasu, 2007 ⁴⁷	Outpatient	2003 - 2004	2.08 million visits	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Depression, anxiety	Atypical antipsychotics are being extensively prescribed to children and adolescents: in total, antipsychotics were prescribed in 1% of overall visits by children and adolescents in 2003 - 2004; most (99%) of these visits involved prescribing of atypicals. The most frequently used atypicals were risperidone, quetiapine, and aripiprazole; males and whites were more likely to use these drugs.
Cooper, 2004 ⁴⁸	All	1996 - 2001	6,803	Cohort study	Tennessee	All; not specified	Tourette's, ADHD	New users of antipsychotics nearly doubled from 1996 to 2001; new users of atypicals increased from 6.8% in 1996 to 95.9% in 2001. New use for ADHD increased 2.5-fold, while new use for Tourette and autism remained stable.
Halloran, 2010 ⁵⁰	Inpatient and Outpatient	2002 - 2005	172,766	Private insurance claim data analysis	Nationally representative	All	Anxiety	The one-year prevalence of atypical antipsychotics use in children increased persistently, from 7.9 per 1,000 in 2002 to 9.0 per 1,000 in 2005. Boys were 2 times more likely than girls to receive atypical antipsychotics. The most common conditions were disruptive behavior disorders, mood disorders, and anxiety. Most children had more than one psychiatric diagnosis.

Table 2. Large utilization studies in the United States (continued)

Author/ Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Olfson, 2006 ⁴⁶	Outpatient	1993 - 2002	1,224,00 0 visits	Survey data analysis	Nationally representative	All; not specified	All; not specify off-label	Atypical antipsychotics are widely prescribed among children and adolescents; a sharply increased use of atypical antipsychotics was found from 2000 to 2002, composing 92.3% of the antipsychotics prescribed in office-based practice.
Patel, 2006 ⁷⁶	Outpatient	1998 - 2001	7,353	Drug claims review	Texas	All; not specified	Anxiety, depression, ADHD, substance use disorder	Disruptive behavioral disorders, depressive disorders, and bipolar disorders accounted for the top three conditions associated with children and adolescents receiving antipsychotics.
Pathak, 2010 ⁴⁹	Outpatient	2001 - 2005	11,700	Medicaid claim data analysis	Arkansas	Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone	ADHD, depression, anxiety, eating disorders, OCD, personality disorders, PTSD, tic disorders, substance abuse	The number of children receiving atypical antipsychotics doubled during the study period, and the prescriptions were largely unsupported by evidence from clinical studies. The most common condition was ADHD, followed by depression, conduct disorder, oppositional defiant disorder, and adjustment reactions.

ADHD = attention-deficit hyperactivity disorder; ED = emergency department; FDA = Food and Drug Administration; MD = doctor; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder

Note: In the table, we excluded five articles that examined mainly adverse events, and eight articles that focused on either utilization of other drugs such as typicals/antidepressants or utilization for on-label conditions or both. We did not include articles examining utilization patterns in countries other than the United States.

Discussion

Most of the utilization studies used national representative survey data or claim data, and their findings reflect national trends. Various settings were covered, including long-term care facilities, communities, inpatient and outpatient settings, VA, and emergency department. We found more studies on some drugs (e.g., risperidone, quetiapine, and olanzapine) than others (we found none on recently approved atypicals asenapine, iloperidone, and paliperidone), more studies on some conditions (e.g., dementia, depression, PTSD and anxiety) than others (e.g., insomnia, eating disorder, and obsessive-compulsive disorder [OCD]), and more studies on the elderly than other populations.

The majority of these studies also investigated the utilization/prescription patterns of other drugs (e.g., conventional antipsychotics, antidepressants, other neuroleptics) simultaneously, and many of them did not distinguish on-label and off-label uses. Still, a high prevalence and a rapid increase in off-label use of the atypical agents have been observed, both in the United States and internationally. Importantly, a study of over 350,000 records indicated that more atypicals than conventional antipsychotics and combinations were used at U.S. ambulatory care visits³⁵ by patients with mental health disorders in the period from 1996 to 2003. Some articles pointed out that despite the scarce evidence supporting efficacy of such uses, the atypicals had been widely prescribed among different populations.

Only a handful of articles examined prescription patterns by gender and by racial/ethnic group. Although a couple of them found that males and whites were more likely to receive off-label prescription of atypicals, the lack of information could not lead to a solid conclusion on whether or not there exist sociodemographic disparities.

The utilization studies covered mostly 1996 to 2004; only a few were conducted after the 2005 FDA and Health Canada warnings on possible severe adverse events in the elderly. One recent study indicated that the 2005 regulatory warning was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. However, the prevalence of off-label use of atypical drugs remains high. We conclude that more studies are needed to document the most recent off-label prescription patterns of atypical antipsychotics, especially the newly approved ones, ideally by different sociodemographic populations and by individual off-label indications.

Key Question 2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

Sub-Key Question 2. How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications?

Key Points

We found no trials of paliperidone, asenapine, or iloperidone for off-label uses.

Attention deficit-hyperactivity disorder (ADHD). This off-label use was not included in our 2006 evidence report.

We found three placebo controlled trials (PCTs) and one active-control trial for ADHD.

One trial found risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P) in children with no serious co-occurring disorders.

Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores compared with placebo in children with bipolar disorder and ADHD.

One trial found risperidone led to greater reduction in SNAP-IV scores than methylphenidate in mentally retarded children with ADHD.

There were no trials of quetiapine, olanzapine, or ziprasidone for ADHD.

Anxiety. This off-label use was not included in our 2006 evidence report.

One recently published systematic review found quetiapine monotherapy superior to placebo for generalized anxiety disorder (GAD), as measured by improvement in the Hamilton Anxiety Scale (HAM-A).

We found 14 PCTs of atypicals for anxiety. Three trials of quetiapine monotherapy for GAD were clinically similar enough to pool; relative risk of responding on the HAM-A favored quetiapine over placebo. There were not enough trials of olanzapine, risperidone, or ziprasidone to pool; these trials had mixed results.

One trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each showed no difference in efficacy between quetiapine and paroxetine or escitalopram.

There were no trials of aripiprazole for anxiety disorders.

Dementia. Our 2006 CER focused on two published meta-analyses on use of atypicals in elderly patients with dementia. They found small but statistically significant effects for treatment with risperidone and aripiprazole, and trends toward efficacy of olanzapine and quetiapine.

The number of new trials published since 2006 justified conducting our own new meta-analyses.

In our pooled analysis of efficacy in treating overall behavioral symptoms such as aggression, motor activity and hostility, aripiprazole, olanzapine, and risperidone were superior to placebo as measured by total scores on BEHAVE-AD, Brief Psychiatric Rating Scale (BPRS), and Neuropsychiatric Inventory Scale (NPI).

Risperidone (six PCTs) was superior to placebo in decreasing psychosis symptoms such as delusions and hallucinations in elderly patients with dementia. Results for aripiprazole (three PCTs) did not meet conventional levels of statistical significance.

In our pooled analysis on agitation outcomes, aripiprazole (two PCTs), olanzapine (four PCTs), and risperidone (six PCTs) were superior to placebo.

There were no trials of ziprasidone in dementia patients.

Three head-to-head trials compared atypicals for dementia; none was found superior.

We pooled five head-to-head trials of atypicals versus haloperidol; there was no statistical difference in effect. There were too few trials to pool by specific atypical. One trial found no difference in effect between risperidone and topiramate.

Depression—major depressive disorder (MDD). Our 2006 CER reported that atypicals were not more effective as augmentation to selective serotonin reuptake inhibitors than placebo at 8 weeks. However, in some trials they led to more rapid improvement (2 to 4 weeks).

Meta-analyses published in 2007 and 2009 found atypicals superior to placebo in increasing response and remission rates, and found no statistical difference between specific atypicals.

By 2011, new trials augmenting selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) with atypicals had been conducted and published. We conducted new meta-analyses that showed that several atypicals have efficacy in treatment of depression when used as augmentation and that quetiapine is effective as monotherapy.

In our pooled analysis, the relative risk of responding on Hamilton depression (HAM-D) scores for participants taking quetiapine (three PCTs) or risperidone (three PCTs) as augmentation was significantly higher than for those taking placebo.

Other trials reported the Montgomery-Asberg Depression Rating Score (MADRS); the relative risk of responding for participants taking aripiprazole (three PCTs) was significantly higher than for placebo. Risperidone was only included in one PCT that reported MADRS; the drug was statistically superior to placebo. One PCT of ziprasidone reported MADRS outcomes; results were statistically superior to placebo.

The three olanzapine PCTs (included in our original 2006 report) found the drug inefficacious as monotherapy for MDD. Since then, five trials of quetiapine monotherapy have been reported. We conducted a meta-analysis of these trials; the relative risk of remitting on the MADRS was statistically superior for quetiapine compared with placebo.

One trial found quetiapine superior to lithium to HAM-D and MADRS scores.

No head-to-head trials of atypicals for MDD were found.

Eating disorders. This off-label use was not included in our 2006 report.

Five trials of olanzapine were found; three reporting body mass index (BMI) outcomes could be pooled. There was no difference in BMI increase at 1e or 3 months between participants taking olanzapine and those taking placebo. One trial of quetiapine also reported no statistical difference in BMI increase at three months.

There were no trials of aripiprazole, risperidone, or ziprasidone for treatment of eating disorders.

Insomnia. This off-label use was not included in our 2006 report.

We found only one small trial of quetiapine for this use; difference in sleep outcomes was not statistically different from placebo.

Two observational studies of olanzapine and four of quetiapine found promising improvements in sleep quality and sleep onset.

No studies of aripiprazole, risperidone, or ziprasidone for insomnia were found.

Obsessive Compulsive Disorder (OCD). Our 2006 meta-analysis found atypicals had a clinically important benefit when used as augmentation to SSRIs.

Three published meta-analyses reported similar findings.

Our 2011 analysis of PCTs reporting Y-BOCS (Yale-Brown Obsessive Compulsive Scale) outcomes showed significant effects for risperidone (three PCTs) as augmentation in treatment of refractory patients. There were too few trials (two) to permit separate pooling for olanzapine; difference in effect versus placebo was statistically insignificant in both studies.

Two new trials found quetiapine superior to placebo as augmentation to citalopram according to Y-BOCS and Clinical Global Impression Scale - Improvement subscale (CGI-I) scores.

No trials of aripiprazole for OCD were found.

One new trial found quetiapine augmentation of an SSRI superior to augmentation with clomipramine.

One head-to-head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation for OCD. Another head-to-head trial found quetiapine had greater efficacy than ziprasidone for this purpose.

Personality Disorders. Our 2006 CER found three trials of olanzapine and one of aripiprazole for borderline personality disorder (BPD); all reported efficacy of the drug.

Since the original CER was published, PCTs using atypicals for treatment of BPD have shown mixed results. Due to heterogeneity of outcomes, we could not perform a meta-analysis.

Overall, olanzapine had mixed results in seven trials, aripiprazole showed efficacy in two trials, quetiapine had efficacy in one trial, and ziprasidone was found ineffective in one trial.

Risperidone had mixed results when used to treat schizotypal personality disorder in one small trial.

No head-to-head trials of atypicals for personality disorder were found.

Post-traumatic Stress Disorder (PTSD). Our 2006 CER reported on three PCTs of atypicals as augmentation for PTSD in male veterans and three PCTs as monotherapy in abused women. We had insufficient trials to conduct meta-analysis. The trials for combat-related PTSD had beneficial results, while the other trials had mixed results.

One published meta-analysis of risperidone and olanzapine studies found atypicals superior to placebo as measured by change in CAPS score. Results were not separated by drug.

Another review which included open label trials found small positive effects for risperidone and quetiapine compared with placebo.

In 2011, five PCTs were clinically similar enough to pool using the change in Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone (four trials) was superior to placebo. The other trial found olanzapine superior to placebo.

We also found a trial that reported a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared with patients treated with placebo. (This study did not report exact scores, so could not be pooled.)

In our meta-analysis of risperidone treatment by trial length, pooled results from at least 12 weeks followup were not statistically different from those reported at less than 12 weeks.

In our meta-analysis by condition, atypicals showed efficacy in treatment of combat-related PTSD but not PTSD in abused women.

No trials of aripiprazole, or ziprasidone for PTSD were found.

No head-to-head trials of atypicals for PTSD were found.

Substance abuse. This off-label use was not included in our 2006 CER.

We found two PCTs of aripiprazole and one of quetiapine that reported the percent of alcohol abusers completely abstinent during followup period. In our pooled analysis, the drugs had insignificant efficacy compared with placebo.

We pooled two PCTs of olanzapine and one of risperidone in cocaine users. There was no difference in efficacy versus placebo as measured by change in Addiction Severity Index (ASI).

One PCT found aripiprazole ineffective in reducing use of intravenous amphetamine, as measured by urinalysis. Another PCT found aripiprazole ineffective in reducing craving for methamphetamine.

One PCT of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.

One trial of aripiprazole versus naltrexone in alcohol abusers found no difference in either mean number of days abstinent or percentage of participants completely abstinent.

One trial augmenting naltrexone with quetiapine found no difference from placebo augmentation in any alcohol use outcomes.

One trial of risperidone versus pergolide found neither more efficacious than placebo in reducing cocaine use.

There were no head-to-head trials of atypicals for substance abuse.

Tourette's syndrome. No new trials of atypicals have been published since our 2006 CER reported that risperidone was superior to placebo in one small PCT, and it was at least as efficacious as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One PCT of ziprasidone showed variable efficacy compared with placebo.

Detailed Analysis

ADHD. This off-label use was not included in our 2006 systematic review. In 2011 we found no prior meta-analyses or systematic reviews on atypical antipsychotics for ADHD. There were four randomized controlled trials (RCTs); two reported on risperidone and two on aripiprazole. The trials lasted either 4 or 6 weeks. Sample sizes were small, ranging from 16 to 45 participants. Trial quality was adequate; the mean Jadad score was 3.5. We were unable to conduct a meta-analysis due to heterogeneity of the outcomes and populations. The studies are displayed in Table 3.

One risperidone study showed that 100 percent of the patients “responded,” as defined by improving at least 30 percent on CAS-P. This compares WITH 77 percent of the placebo patients.⁷⁷ The other risperidone study⁷⁸ compared risperidone to methylphenidate in children and adolescents with both ADHD and moderate mental retardation. Using SNAP-IV, they found reduced ADHD symptoms with both treatments, with a greater reduction of symptoms with risperidone than methylphenidate. They also found adverse effects of weight gain with risperidone, whereas the other risperidone study had found no weight difference from placebo.⁷⁸

The two studies of aripiprazole involved children with both ADHD and bipolar disorder. Neither showed a difference in ADHD symptoms per the SNAP-IV. One study looked at aripiprazole versus placebo and listed adverse events of somnolence and sialorrhea.⁷⁹ The other compared aripiprazole plus placebo versus aripiprazole plus methylphenidate and included the adverse effect of one patient experiencing a severe bipolar mixed episode while on aripiprazole and methylphenidate.⁸⁰

Table 3. Atypical antipsychotics for ADHD

Study/Type	Treatment	N	Dose/Duration	ADHD-Measures	Effects
Armenteros, 2007 ⁷⁷ /RCT	Risperidone vs Placebo	25	1.08 mg (mean) + psychostimulant/ 4 weeks	CAS-P CAS-T	100% of risperidone patients improved 30% over baseline in CAS-P compared with only 77% of placebo. No change in CAS-T
CorreiaFilho, 2005 ⁷⁸ /RCT	Risperidone vs methylphenidate (ADHD+Mental retardation)	45	2.9 mg (mean)/ 4 weeks	SNAP-IV	Reduced ADHD symptoms in both per SNAP-IV, greater in risperidone than methylphenidate
Tramontina, 2009 ⁷⁹ /RCT	Aripiprazole vs. Placebo (ADHD+Bipolar)	43	6 weeks	SNAP-IV	No difference in ADHD symptoms
Zeni, 2009 ⁸⁰ /RCT	Aripiprazole + methylphenidate or placebo (ADHD+Bipolar)	16	2+2 week crossover	SNAP-IV	No improvement in ADHD symptoms

ADHD = attention-deficit hyperactivity disorder; CAS-P = Children's Aggression Scale-Parent Version; CAS-T = Children's Aggression Scale-Teacher Version; RCT = randomized controlled trial; SNAP-IV = Swanson, Nolan, and Pelham rating scale

Anxiety. Anxiety is also a new clinical topic not included in our 2006 review. We found two prior meta-analyses on use of atypicals for this condition.⁸¹ One combined OCD trials with trials for GAD; thus, we have excluded it. Another found quetiapine monotherapy significantly better than placebo for treatment of generalized anxiety disorder.⁸²

Our literature search identified 18 reports of trials that evaluated the use of olanzapine,^{83,84} quetiapine,⁸⁵⁻⁹⁵ risperidone,⁹⁶⁻⁹⁹ or ziprasidone¹⁰⁰ for the treatment of anxiety. Jadad scores ranged from 2 to 5; mean score was 3.1. Sample sizes varied widely, from 7 to 873. Followup time ranged from same day (for public speaking anxiety) to 1 year. One trial had no placebo comparison group and is discussed under active controlled trials.⁹⁶ Two trials assessed anxiety outcomes in bipolar patients^{92,97} so are considered beyond the scope of this report.

Of the remaining 15 PCTs, all but three^{83,89,95} reported an outcome measure based on the HAM-A. These three trials studied social anxiety. The first of these trials found olanzapine superior to placebo in the treatment of social anxiety disorder;⁸³ the other two studied quetiapine and did not find it superior to placebo.^{89,95}

The remaining 12 PCTs ranged from 6 to 18 weeks in duration. One small pilot of quetiapine augmentation of SSRI/venlafaxine versus placebo augmentation was not considered further for analysis due to heterogeneity. This study⁸⁶ included patients with major depression and comorbid anxiety.

Six remaining PCTs assessed quetiapine or quetiapine augmentation, two evaluated risperidone or risperidone augmentation,^{98,99} one assessed olanzapine⁸⁴ and one studied ziprasidone.¹⁰⁰ These trials either reported the mean score on the HAM-A or the percent of participants that responded to treatment as measured by the HAM-A. Since trials did not consistently report the information needed to calculate a weighted mean difference for pooling of the HAM-A total score, we used the number of participants that responded to treatment as the outcome to pool. The trials defined 'responders' as participants who decreased their HAM-A score by at least 50 percent.

The one ziprasidone PCT¹⁰⁰ and two PCTs of quetiapine^{85,93} did not report the percent or count of participants that responded to treatment and thus could not be pooled. The first of these

quetiapine trials used the drug as augmentation of paroxetine for the treatment of refractory generalized anxiety disorder. This study did not find a significant benefit for quetiapine over placebo augmentation.⁸⁵ The second studied quetiapine monotherapy for maintenance treatment of generalized anxiety disorder and found a reduced risk of relapse of anxiety events compared with placebo.⁹³ The ziprasidone PCT¹⁰⁰ reported no difference in HAM-A score at 8 weeks, compared with placebo.

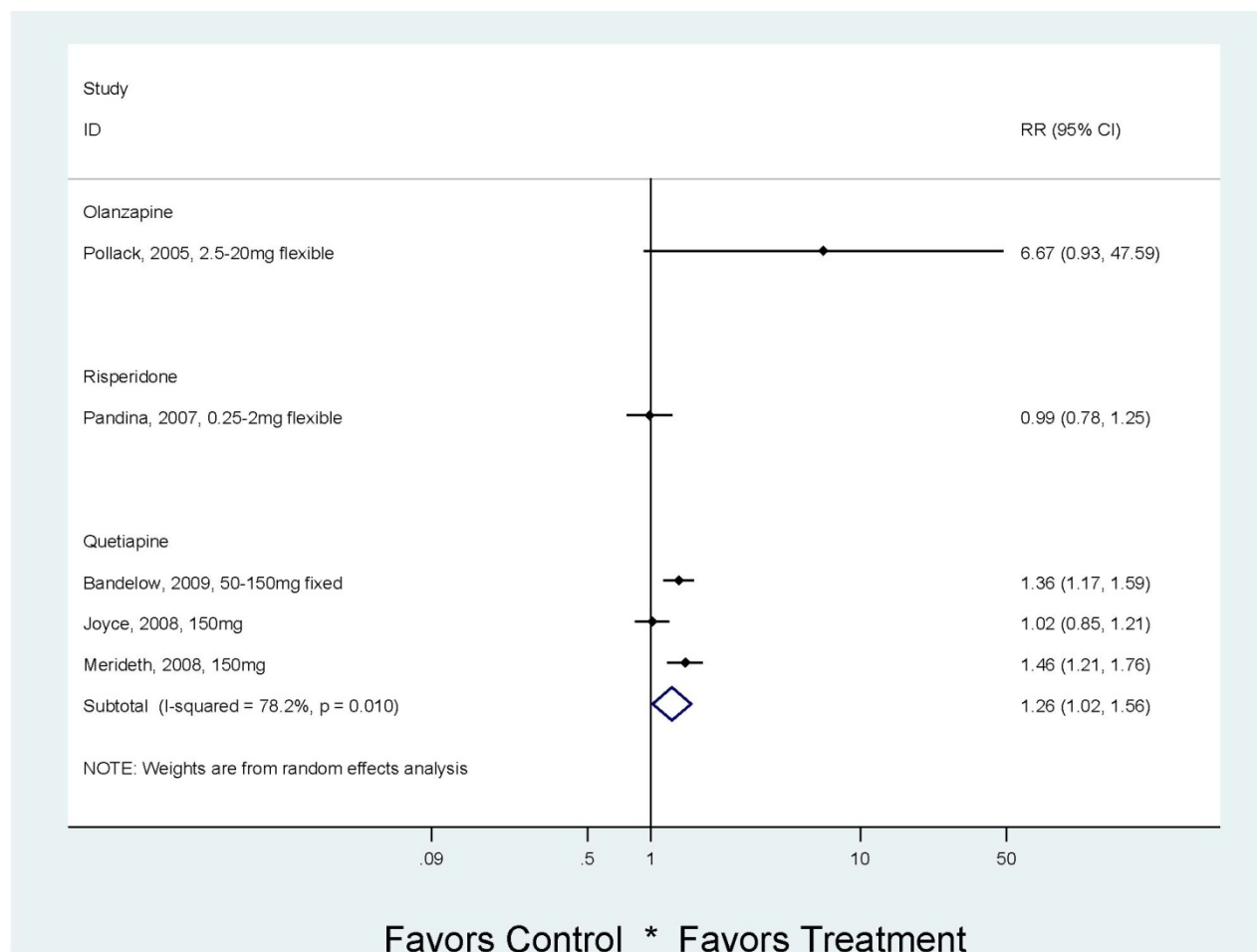
We separated the augmentation studies from studies of monotherapy. One small (N=20) study found quetiapine augmentation of SSRI resulted in more responders on the HAM-A than placebo augmentation (60 percent versus 30 percent) but this difference was not statistically significant.⁹⁰ A similar larger study (N=409) found no statistical difference in HAM-A response rate at eight weeks.⁹¹ The remaining three trials of quetiapine monotherapy versus placebo listed in Table 4, were pooled.^{87,88,94} The trials were similar in size, ranging from 710 to 873 participants, and all had a quetiapine 150mg comparison group that was used in the analysis. The results are displayed in Figure 3, along with the olanzapine and risperidone PCTs. The pooled estimate of the relative risk of responding on the HAM-A was 1.26 (95% confidence interval [CI] 1.02, 1.56) in favor of the quetiapine groups. Resulting NNT (number needed to treat) is eight for one responder as measured by HAM-A. The I-squared statistic was 74.4 percent, indicating heterogeneity. Neither Begg's nor Egger's test for publication bias indicated the presence of bias (p=0.462, p=0.239, respectively).

Table 4. Generalized anxiety disorder—PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Pollack et al. 2006 ⁸⁴	18-72 years old, DSM-IV GAD comorbid depression, dysthymia, and other anxiety disorders except for PTSD and OCD, if GAD was considered primary by the clinician and patient based on disorder severity and associated distress	24	Placebo Olanzapine 2.5-20 mg/day	6 weeks	% Responders on HAM-A: Olanzapine vs Placebo - RR = 6.67 (0.93 , 47.59)
Bandelow et al. 2009 ⁸⁸	18-65 years old, diagnosed GAD, HAM-A total score ≥ 20 with item 1 and 2 scores ≥ 2 , MADRS total score ≤ 16 , CGI-S score ≥ 4 at enrolment and randomization	873	Placebo Quetiapine 50-150 mg/day Quetiapine 50 mg/day Paroxetine 20 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - RR = 1.36 (1.17 , 1.59)
Joyce et al. 2008 ⁹⁴	Diagnosed GAD	710	Placebo Quetiapine 50 mg/day Quetiapine 150 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - RR = 1.02 (0.85 , 1.21)
Merideth et al. 2008 ⁸⁷	DSM-IV diagnosis of GAD, HAM-A total score ≥ 20 with item 1 and item 2 scores ≥ 2 , CGI-S ≥ 4 , MADRS ≤ 16	854	Placebo Escitalopram 10 mg/day Quetiapine 150 mg/day Quetiapine 300 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - RR = 1.46 (1.21 , 1.76)
Pandina et al. 2007 ⁹⁹	15-65 years old, diagnosed GAD, CGI-S ≥ 4 , antidepressant, benzodiazepine, buspirone or a combination of an antidepressants plus benzodiazepine or buspirone for at least 8 weeks prior and stable x 4 weeks	417	Placebo 0.25-2 mg/day Risperidone 0.25-2 mg/day	4 weeks	% Responders on HAM-A: Risperidone vs Placebo - RR = 0.99 (0.78 , 1.25)

CGI-S = Clinical Global Impression Scale-Severity Subscale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; RR = relative risk

Figure 3. Anxiety % responders on Hamilton Anxiety Scale



Active Controlled Trials. An 8-week head-to-head trial of risperidone and paroxetine for panic attacks found statistically significant improvements in the HAM-A for both groups and no difference between treatment groups on several other anxiety measures.⁹⁶

Two of the trials in our meta-analysis also had “active” arms. One trial found 50 or 150 mg/day quetiapine as effective at 8 weeks as paroxetine 20 mg/day, but with fewer sexual side effects.⁸⁸ Another trial⁸⁷ found 150 or 300 mg/day quetiapine as effective as 10 mg/day escitalopram at eight weeks.

Dementia. Our 2006 systematic review reported on two published meta-analyses assessing risperidone, quetiapine, and olanzapine for symptoms of dementia in the elderly,^{101,102} and one additional meta-analysis solely on risperidone.¹⁰³ In summary, they found small but statistically significant effects for treatment with risperidone and aripiprazole, and trends toward efficacy of olanzapine and quetiapine. Since 2006, one new meta-analysis¹⁰⁴ found no statistically or clinically significant difference between atypicals and placebo. In 2010, we were able to conduct new meta-analyses that included all trials from the previously published analyses plus several newer trials.

We reviewed 38 total trials on dementia. Twenty-seven trials compared an atypical to placebo: five aripiprazole,¹⁰⁵⁻¹⁰⁹ ten olanzapine,¹¹⁰⁻¹¹⁹ six quetiapine,¹¹⁹⁻¹²⁴ and eight

risperidone.^{115,116,119,125-129} One trial¹²⁰ was later determined to be a duplicate report of a published article¹²⁴ and thus excluded, leaving 37 trials total. Thirteen trials compared an atypical to another active drug.^{112,121,124,125,130-138} Two compared atypical in general to placebo.^{139,140} Four trials compared one atypical drug to another;^{116,119,141,142} two are also included in our PCT analyses. Two compared the continuation of an atypical to a cessation group.^{143,144} The quality of the trials varied widely, with Jadad scores ranging from zero to five; mean score was 3.0. Mean sample size was 242; range was 16 to 815. Most studies employed flexible dosing, as displayed in Figure 4 to 6. Followup times ranged from same day to 1 year.

Seventeen PCTs reported outcomes between 6 and 12 weeks; this range was considered sufficiently clinically similar to pool. These PCTs are described in detail in Table 5. We grouped study outcomes into three categories: total/global scores, psychosis, and agitation.

Total global score includes psychiatric symptoms of delusions, suspiciousness, dysphoria, anxiety, motor agitation, aggression, hostility, euphoria, disinhibition, irritability and apathy, as measured by the NPI. Psychosis was measured by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS, and NPI, which focus primarily on delusions and hallucinations. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory, and included the symptoms physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.

Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2, 5, and 10 mg arm. We present the results by dosage later in the relevant section (Key Question 5).

There was a positive, significant difference between the atypicals as a class and placebo for all three outcome measures: total/global scores (standardized mean difference [SMD] 0.17 [95% CI 0.08, 0.25]), psychosis (SMD 0.12 [95% CI 0.04, 0.19]), and agitation (SMD 0.20 [95% CI 0.12, 0.27]). While the minimum clinically important difference is not known, these effect sizes are generally considered “small” in magnitude. The I-squared values indicated moderate heterogeneity (range 30.3 percent–53.1 percent). Results are displayed in Figures 4 to 6.

For aripiprazole, olanzapine, and risperidone, the pooled estimate of effect on the total/global score was statistically significant, with an effect size of between 0.12 and 0.20. The pooled estimate of effect for quetiapine was similar (0.13) but this was not statistically different from zero. This effect size is “small.” Corroborating this conclusion is the observation that the mean difference in the pooled NPI total score between treatment and placebo was 3.41 points, which is close to the minimum clinically observable change of 4 points.¹⁴⁵ Individual studies suggested that higher dose of aripiprazole (10mg/day)¹⁰⁷ or risperidone (2mg/day)¹²⁷ were possibly more effective than lower doses, although these findings have not been replicated, dose effects are not addressed in many trials, and dose-response trends across studies are inconsistent. Only the pooled analysis for risperidone had substantial heterogeneity (I-squared = 74.6 percent). There was no evidence of publication bias. Only risperidone had enough studies to conduct a sensitivity analysis based on quality; no difference was found. For treatment of psychosis, results favored risperidone when compared with placebo. As measured by the psychosis subscale of the NPI, pooled estimate of SMD in effect size was 0.20 (95% CI 0.05, 0.36) for risperidone (five trials). Results for aripiprazole (three trials), olanzapine (five trials), and quetiapine (three trials) did not meet conventional levels of statistical significance. Standardized mean difference for

aripiprazole was 0.14 (95% CI -0.02, 0.29), for olanzapine was 0.05 (95% CI -0.07, 0.17) and for quetiapine 0.04 (95% CI -0.11, 0.18).

Pooled estimates of SMD in effect size for agitation were 0.19 (95% CI 0.07, 0.31) for olanzapine (four trials), and 0.22 (95% CI 0.09, 0.35) for risperidone (six trials); once again these trials are generally considered “small” effects. Two trials of aripiprazole reported positive results. Results for quetiapine (five studies) were not significant.

Active Controlled Trials. We conducted a meta-analysis by pooling five trials that compared atypicals to haloperidol on total score.^{124,125,132,133,136} Information from these trials is displayed in Table 6. Difference between atypicals and haloperidol was not significant. There were too few trials to pool results separately by drug. Regarding psychosis symptoms, we found one trial which showed no difference in efficacy between olanzapine and haloperidol. Results are displayed in Figures 7 and 8. We also found one trial of risperidone versus olanzapine¹³⁸ for dementia. Differences in total/global score and agitation score were not statistically significant.

Head-to-head Trials. Three head-to-head trials, described in Table 7, compared atypicals on total/global scores and psychosis outcomes.^{116,119,142} None was found superior. Results are displayed in Figures 9 to 11.

Table 5. Dementia—PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Breder et al. 2004 ¹⁴⁶	Psychosis/psychotic features, Nursing home resident, NPI or NPI/NH >= 6 sum of hallucinations and delusional items, Age 55-95, MMSE = 6-22	487	Placebo	10 weeks	Total/Global Scores: Aripiprazole vs. Placebo-SMD =0.15 (-0.06, 0.36)
			Aripiprazole 5 mg/day		Psychosis score: Aripiprazole vs Placebo-SMD = 0.20 (-0.01, 0.41)
			Aripiprazole 2 mg/day		Agitation score: Aripiprazole vs Placebo-SMD = 0.27 (0.05, 0.48)
DeDeyn et al. 2003 ¹⁰²	AD with psychosis	208	Placebo	10 weeks	Total/Global Scores Aripiprazole vs Placebo - SMD =0.06 (-0.21, 0.34)
			Aripiprazole 2–15 mg/day		Psychosis score: Aripiprazole vs Placebo-SMD = 0.16 (-0.12, 0.43)
Mintzer et al. 2007 ¹⁰⁷	Diagnosed with AD and delusions / hallucinations. Institutionalized, capable of self-locomotion, MMSE 6-22. NPI-NH score >=6	487	Placebo	10 weeks	Total/Global Scores Aripiprazole vs Placebo - SMD = 0.16 (-0.05, 0.37)
			Aripiprazole 2 mg/day		Psychosis score: Aripiprazole vs Placebo-SMD =0.24 (0.03, 0.45)
			Aripiprazole 5 mg/day		Agitation score: Aripiprazole vs Placebo-SMD = 0.31 (0.10, 0.52)
			Aripiprazole 5-10 mg/day		

Table 5. Dementia—PCTs contributing to meta-analyses (continued)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Streim et al. 2004 ¹⁴⁷	AD with psychosis, Age 55-95, MMSE = 6-22, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items, hallucinations and delusions ≥ 1 month	256	Placebo	10 weeks	Total/Global Scores Aripiprazole vs Placebo - SMD = 0.36 (0.11, 0.61)
Streim et al. 2008 ¹⁰⁸			Aripiprazole 8.6 mg/day		Psychosis score: Aripiprazole vs Placebo-SMD = -0.02 (-0.27, 0.23) Agitation score: Aripiprazole vs Placebo-SMD = 0.30 (0.05, 0.55)
DeDeyn et al. 2004 ¹¹¹	Age ≥ 40, Hospitalized/institutionalized, Psychosis/psychotic features, MMSE = 5-26	NR	Placebo Olanzapine 1.0 mg/day Olanzapine 2.5 mg/day Olanzapine 5.0 mg/day Olanzapine 7.5 mg/day	10 weeks	Total/Global Scores Olanzapine vs Placebo - SMD = 0.14 (-0.05, 0.34) Psychosis score: Olanzapine vs Placebo-SMD = 0.17 (-0.02, 0.37) Agitation score: Olanzapine vs Placebo-SMD = 0.14 (-0.05, 0.33)
Deberdt et al. 2004 ¹¹⁶	Age ≥ 40, AD, vascular or mixed dementia, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items	494	Placebo Olanzapine 5.2 mg Risperidone 1.0 mg	10 weeks	Total/Global Scores Olanzapine vs Placebo - SMD = -0.02(-0.27, 0.23) Total/Global Scores Risperidone vs Placebo - SMD = -0.13 (-0.38, 0.12) Psychosis score: Olanzapine vs Placebo-SMD = -0.12 (-0.36, 0.13) Risperidone vs Placebo-SMD = -0.03 (-0.34, 0.16) Agitation score: Olanzapine vs Placebo-SMD = 0.09 (-0.16, 0.34) Risperidone vs Placebo-SMD = 0.14 (-0.11, 0.39)
Kennedy et al. 2005 ¹¹⁸	Age ≥ 40, MMSE 14-26	268	Placebo Olanzapine 2.5-7.5 mg/day	26 weeks	Psychosis score: Olanzapine vs Placebo-SMD = -0.07 (0.33, 0.18)

Table 5. Dementia—PCTs contributing to meta-analyses (continued)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Schneider, et al. 2006 ¹⁴⁸	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on (BPRS), ambulatory and living at home or in an assisted-living facility	421	Placebo	12 weeks	Total/Global Scores Olanzapine vs Placebo - SMD =0.15 (-0.11, 0.40)
Sultzer et al. 2008 ¹¹⁹			Olanzapine 5.5mg/day		Quetiapine vs Placebo - SMD = 0.15 (-0.11, 0.40)
			Quetiapine 56.5 mg/day		Risperidone vs Placebo - SMD =0.40 (0.13, 0.68)
			Risperidone 1.0 mg/day		Psychosis score: Olanzapine vs Placebo-SMD =0.07 (-0.19, 0.33)
					Quetiapine vs Placebo- SMD =0.16 (-0.10, 0.42)
					Risperidone vs Placebo- SMD =0.38 (0.11, 0.66)
					Agitation score: Olanzapine vs Placebo- SMD =-0.28 (0.02, 0.53)
		Quetiapine vs Placebo- SMD =0.20 (-0.06, 0.46)			
		Risperidone vs Placebo- SMD =0.10 (-0.17, 0.37)			
Street et al. 2000 ¹¹⁰	Possible or probable AD, NPI/NH ≥ 3	206	Placebo	6 weeks	Total/Global Scores Olanzapine vs Placebo - SMD = 0.30 (-0.03, 0.63)
			Olanzapine 5 mg/day		Psychosis score: Olanzapine vs Placebo- SMD =-0.17 (-0.17, 0.50)
			Olanzapine 10 mg/day		Agitation score at 9 weeks: Olanzapine vs Placebo- SMD =0.39 (0.05, 0.72)
			Olanzapine 15 mg/day		
Ballard et al. 2005 ¹²¹	CMAI >= 39, Age >= 60, NPI >= 4	93	Placebo	26 weeks	Agitation score: Quetiapine vs Placebo- SMD =-0.13 (-0.66, 0.39)
			Rivastigmine min 9 mg/day Quetiapine 100 mg/day		
Paleacu et al. 2008 ¹²³	AD with BPSD, age > 50, MMSE < 24, NPI > 6 on any item	40	Placebo	6 weeks	Agitation score: Quetiapine vs Placebo- SMD =-0.48 (-1.11, 0.15)
			Quetiapine 50-300 mg/day		

Table 5. Dementia—PCTs contributing to meta-analyses (continued)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Tariot et al. 2006 ¹²⁴	Diagnosed with DSM-IV AD, > 64 years old, not bedridden, nursing home residents for >= 2 weeks, presence of psychosis, BPRS scores >=24, CGI-S scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPI-NH, scores of >= 5 on MMSE	284	Placebo Haloperidol 0.5-12 mg/day Quetiapine 25-600 mg/day	10 weeks	Total/Global Scores Quetiapine vs Placebo - SMD =0.22 (-0.07, 0.28) Agitation score: Quetiapine vs Placebo- SMD =0.24 (-0.05, 0.54) Psychosis score: Quetiapine vs. Placebo – SMD = 0.00 (-0.29, 0.30)
Zhong et al. 2004 ¹⁴⁹	Institutionalized, diagnosed possible	333	Placebo	10 weeks	Total/Global Scores Quetiapine vs Placebo - SMD =0.04 (-0.21, 0.28)
Zhong et al. 2007 ¹²²	AD or vascular dementia, age >= 55, ambulatory, agitation that didn't result directly from participants medical condition, PANSS-EC total >= 14, one of the 5 PANSS-EC items >= 4.		Quetiapine 100 mg/day Quetiapine 200 mg/day		Psychosis score: Quetiapine vs Placebo - SMD =-0.03 (-0.27, 0.21) Agitation score: Quetiapine vs Placebo - SMD =-0.03 (-0.27, 0.21)
Brody et al. 2003 ¹²⁶	Age >= 55, FAST > 4, MMSE <= 23,	345	Placebo 1.06 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - SMD = 0.46 (0.23, 0.69)
Brody et al. 2005 ¹⁵⁰	CMAI score of >= 4 on at least 1 aggressive item or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3, Nursing home resident, Resident >= 1 month prior to enrollment		Risperidone 0.95 mg/day		Psychosis score: Risperidone vs Placebo- SMD =0.36 (0.13, 0.59) Agitation score: Risperidone vs Placebo- SMD =0.37 (0.14, 0.59)

Table 5. Dementia—PCTs contributing to meta-analyses (continued)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Dedeyn et al. 1999 ¹²⁵	Age >= 55, Hospitalized/institutionalized, FAST >= 4, MMSE <= 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD >= 8	344	Placebo Haloperidol 1.2 mg/day Risperidone 1.1 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - SMD =0.12 (-0.14, 0.38) Agitation score: Risperidone vs Placebo- SMD =0.31 (0.05, 0.57)
Katz et al. 1999 ¹²⁷	Age >= 55, FAST >= 4, MMSE <= 23, BEHAVE-AD >= 8, BEHAVE-AD global rating >= 1	625	Placebo Risperidone 0.5 mg/day Risperidone 1 mg/day Risperidone 2 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - SMD = 0.32 (0.11, 0.53) Psychosis score: Risperidone vs Placebo- SMD =0.20 (-0.01, 0.41) Agitation score: Risperidone vs Placebo- SMD =0.38 (0.17, 0.60)
Mintzer et al. 2006 ¹²⁹	>= 55 years old, residents of nursing homes or long-term care facilities, mobile, met the criteria for psychosis of AD, in need of treatment with an atypical antipsychotic, scored >=2 on any item of the BEHAVE-AD psychosis subscale, MMSE 5-23	473	Placebo Risperidone 0.5-2.5 mg/day	8 weeks	Total/Global Scores: Risperidone vs Placebo - SMD =-0.01 (-0.21, 0.18) Psychosis score: Risperidone vs Placebo- SMD =0.17 (-0.02, 0.36) Agitation score: Risperidone vs Placebo- SMD =0.04 (-0.16, 0.23)

AD = Alzheimer's disease; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Scale; BPRS = Brief Psychiatric Rating Scale; BPSD = Behavioral and Psychological Symptoms of Dementia; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; FAST = ; MMSE = Mini Mental Status Exam; PANSS-EC = Positive and Negative Syndrome Scale-Excited Component; SMD = standardized mean difference

Figure 4. Dementia placebo comparisons—total/global scores

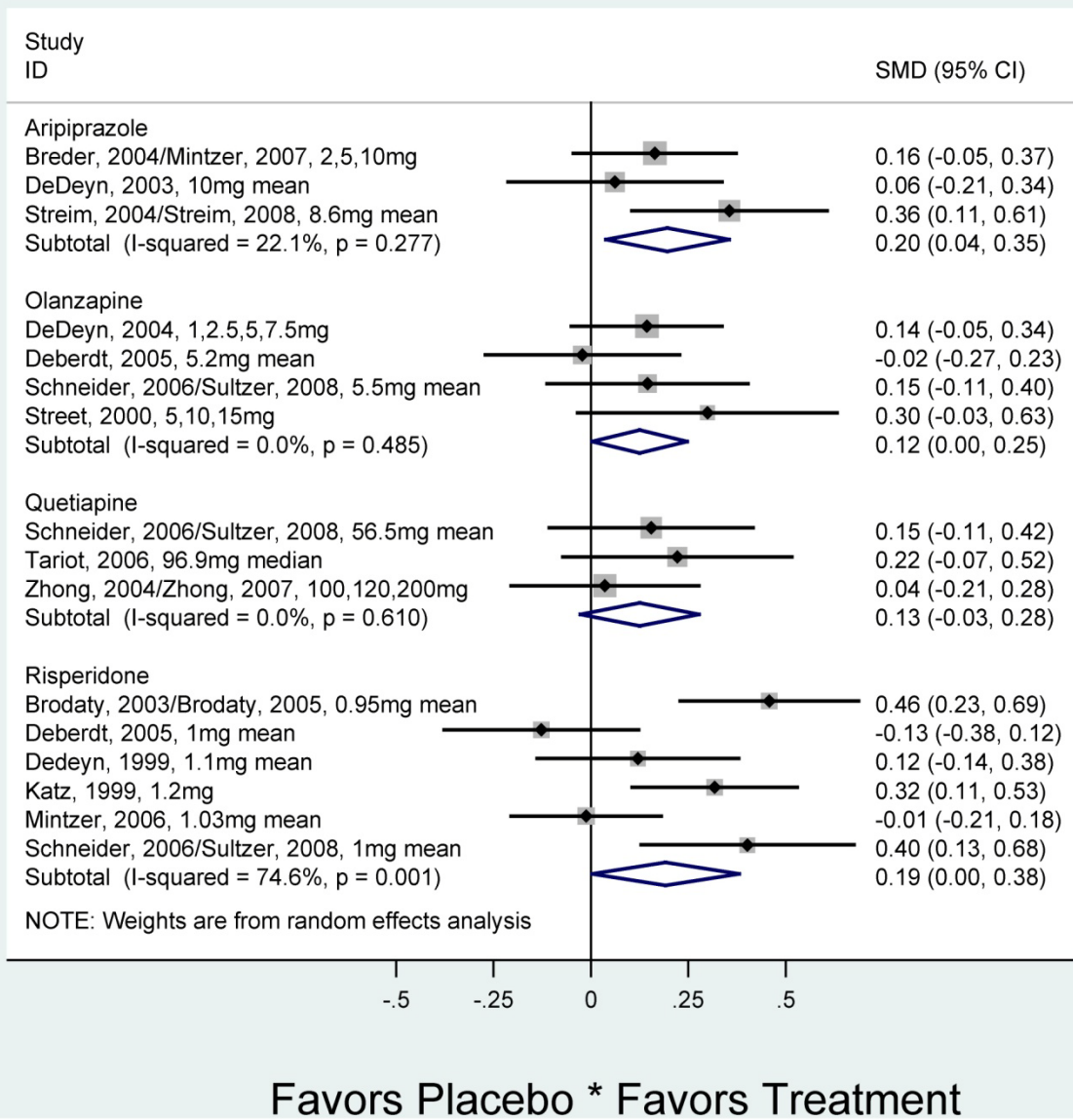


Figure 5. Dementia placebo comparisons—psychosis

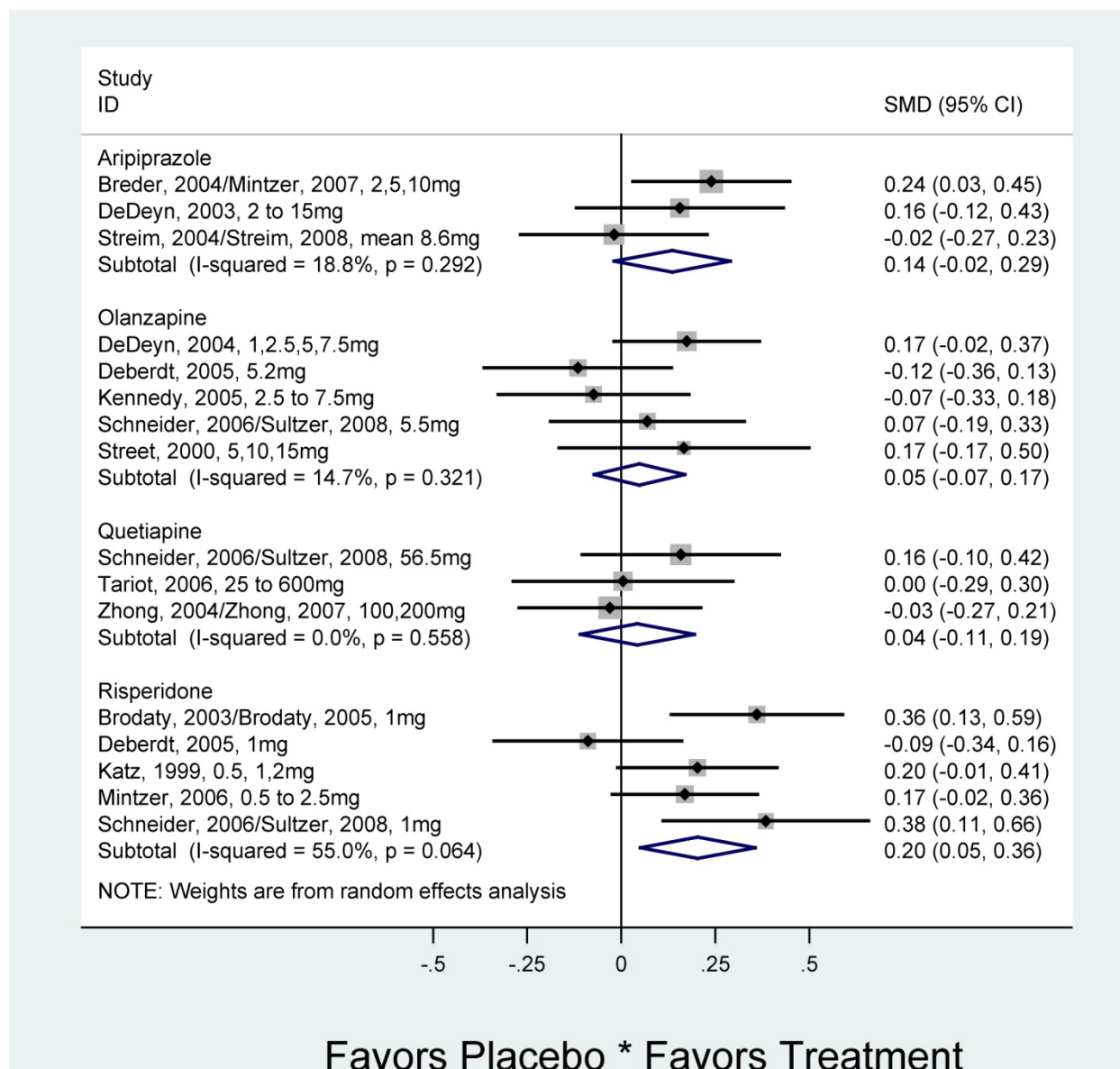


Figure 6. Dementia placebo comparisons—agitation

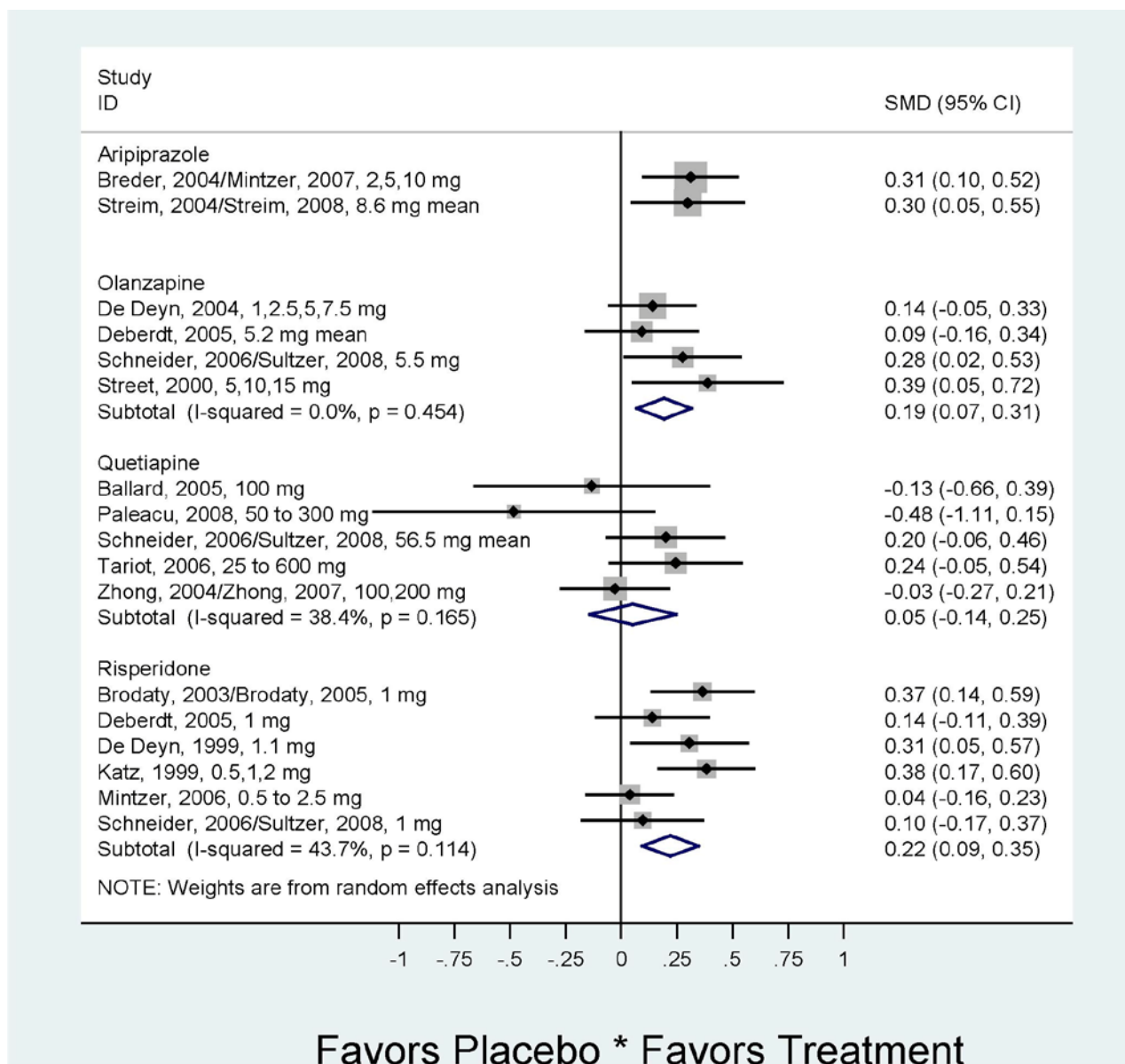


Table 6. Dementia atypical versus haloperidol—PCTs contributing to analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Moretti et al. 2005 ¹³²	DSM-IV for dementia, MMSE ≥ 14, probable VaD, 71-92	256	Typical antipsychotics 10 drops/day	12 months	Total/Global score: Olanzapine vs Haloperidol – SMD = 0.38 (0.17 , 0.60)
Verhey et al. 2006 ¹³⁶	Age ≥ 60 years, diagnosis of dementia according to DSM-IV, agitation level requiring antipsychotic treatment, no use of antipsychotic treatment within 3 days of inclusion CMAI score ≥ 45	NR	Olanzapine 2.5-7.5 mg/day Haloperidol 1-3 mg/day	5 weeks	Total/Global score: Olanzapine vs Haloperidol – SMD = -0.18 (-0.77 , 0.41) Agitation score: Olanzapine vs Haloperidol – SMD = -0.21 (-0.73 , 0.31)
Savaskan et al. 2006 ¹³³	AD, behavioral symptoms > 65	NR	Haloperidol 0.5-4 mg/day Quetiapine 25-200 mg/day	5 weeks	Total/Global score: Quetiapine vs Haloperidol – SMD = 0.99 (0.10 , 1.88) Agitation score: Quetiapine vs Haloperidol – SMD = 0.06 (-0.78 , 0.89)
Tariot et al. 2006 ¹²⁴	> 64 years old, not bedridden, nursing home residents for ≥ 2 weeks, diagnosed with DSM-IV AD, presence of psychosis, BPRS scores ≥ 24, CGI-S scores ≥ 4, scores of ≥ 3 on two or more BPRS items, frequency scores of ≥ 3 on at least one of the two psychosis items of the NPI-NH, scores of ≥ 5 on MMSE	284	Placebo Haloperidol 0.5-12 mg/day Quetiapine 25-600 mg/day	10 weeks	Total/Global score: Quetiapine vs Haloperidol – SMD = 0.16 (-0.16, 0.47) Agitation score: Quetiapine vs Haloperidol – SMD = 0.04 (-0.26 , 0.34)
Dedeyn et al. 1999 ¹²⁵	Age ≥ 55, Hospitalized/institutionalized, FAST ≥ 4, MMSE ≤ 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD ≥ 8	344	Placebo Haloperidol 1.2 mg/day Risperidone 1.1 mg/day	12 weeks	Total/Global score: Risperidone vs Haloperidol – SMD = -0.19 (-0.45, 0.07) Agitation score: Risperidone vs Haloperidol – SMD = -0.07 (-0.19, -0.33)

AD = Alzheimer's disease; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression Scale - Severity Subscale; CMAI = Cohen-Mansfield Agitation Inventory; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; FAST = Functional Assessment Staging scale; MMSE = Mini Mental Status Exam; NPI-NH = Neuropsychiatric Inventory, Nursing Home; NR = not reported; SMD = standardized mean difference

Figure 7. Dementia: atypical versus haloperidol—total/global scores

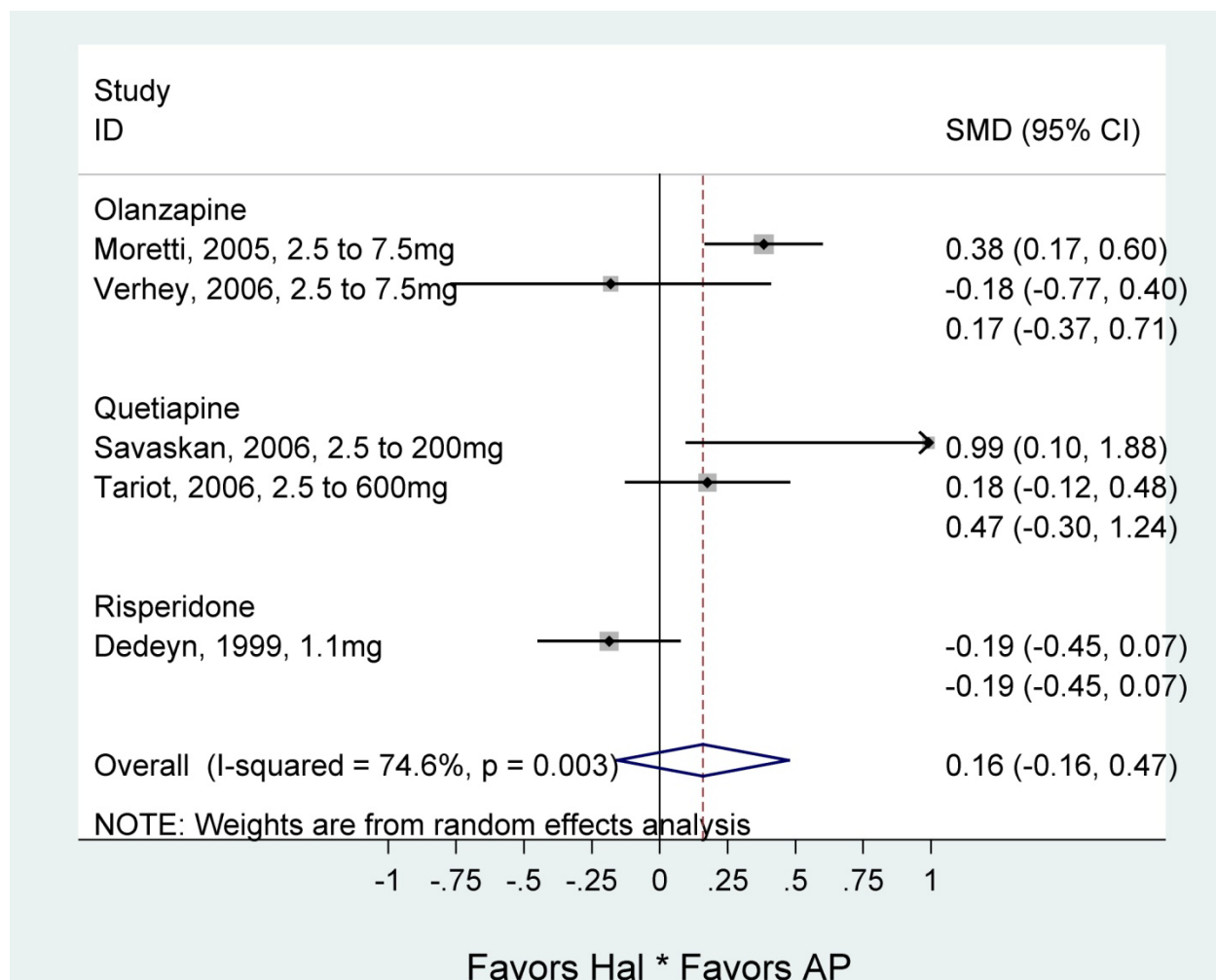


Figure 8. Dementia: atypical versus haloperidol—agitation

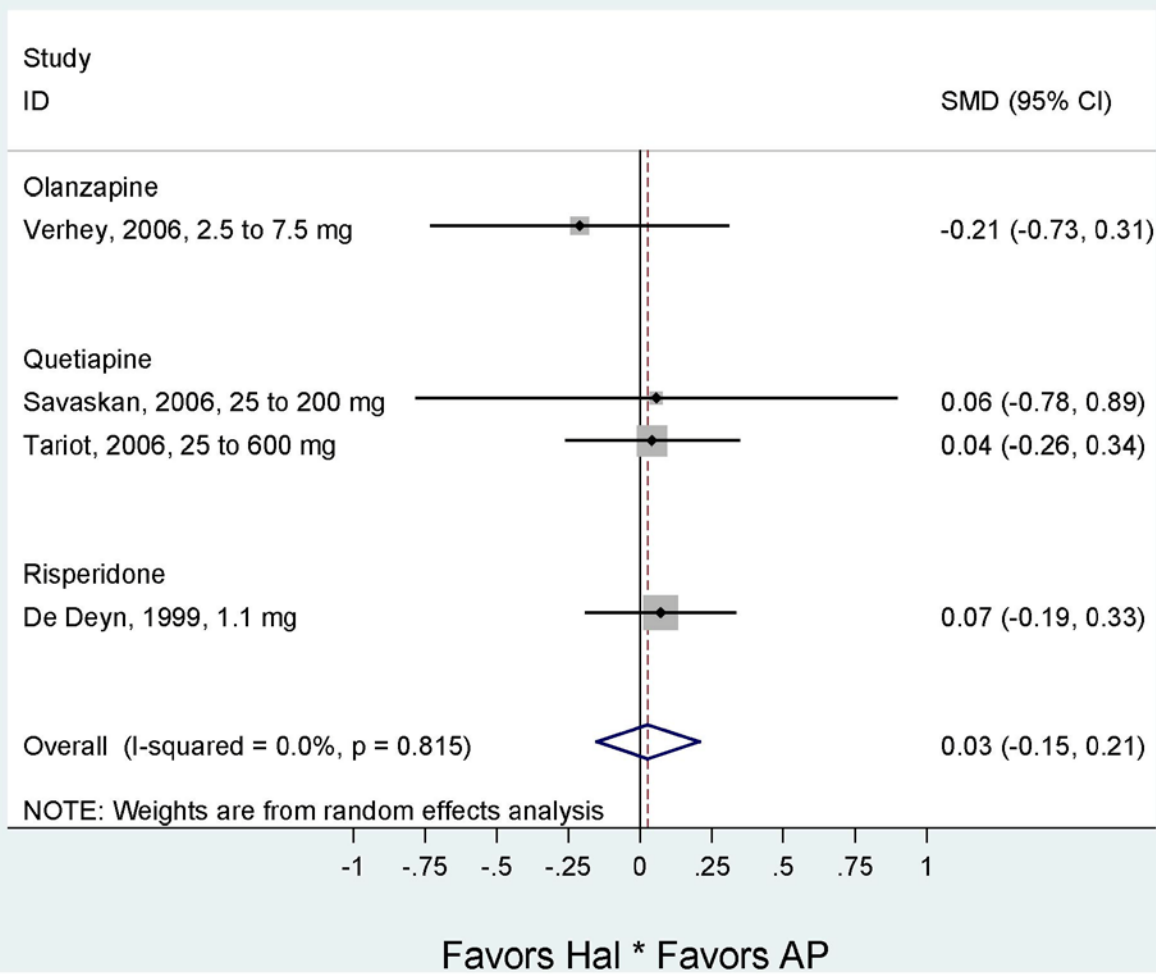


Table 7. Dementia head-to-head studies contributing to analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Deberdt et al. 2004 ¹¹⁶	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items	494	Placebo Olanzapine-5.2 mg Risperidone-1.0 mg	10 weeks	Total/Global score: Olanzapine vs Risperidone-SMD = 0.10 (-0.10, 0.30) Psychosis score: Olanzapine vs Risperidone-SMD = -0.03 (-0.23, 0.17) Agitation score: Olanzapine vs Risperidone-SMD = -0.04 (-0.24, 0.16)
Schneider, et al. 2006 ¹⁴⁸ Sultzer et al. 2008 ¹¹⁹	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on (BPRS), ambulatory and living at home or in an assisted-living facility	421	Placebo Olanzapine 5.5mg/day Quetiapine 56.5 mg/day Risperidone 1.0 mg/day	12 weeks	Total/Global score: Olanzapine vs Risperidone-SMD = -0.27 (-0.56, 0.02) Quetiapine vs Risperidone-SMD = -0.24 (-0.53, 0.06) Psychosis score: Olanzapine vs Risperidone-SMD = -0.27 (-0.56, 0.02) Quetiapine vs Risperidone-SMD = -0.24 (-0.54, 0.05) Agitation score: Olanzapine vs Risperidone-SMD = -0.17 (-0.12, 0.16) Quetiapine vs Risperidone-SMD = 0.10 (-0.20, 0.39)
Rainer et al. 2007 ¹⁴²	55-85 years old, dementia, MMSE score 10-26, have an NPI part I score in sub-items relating to delusions, hallucinations, agitation / aggression	72	Quetiapine 50-400 mg/day Risperidone 0.5-4 mg/day	8 weeks	Total/Global score: Quetiapine vs Risperidone-SMD = -0.06 (-0.55, 0.43) Agitation score: Quetiapine vs Risperidone-SMD = -0.17 (-0.66, 0.32)

AD = Alzheimer's disease; BPRS = Brief Psychiatric Rating Scale; MMSE = ; NPI = Neuropsychiatric Inventory; SMD = standardized mean difference

Figure 9. Dementia head-to-head studies olanzapine or quetiapine versus risperidone—total/global scores

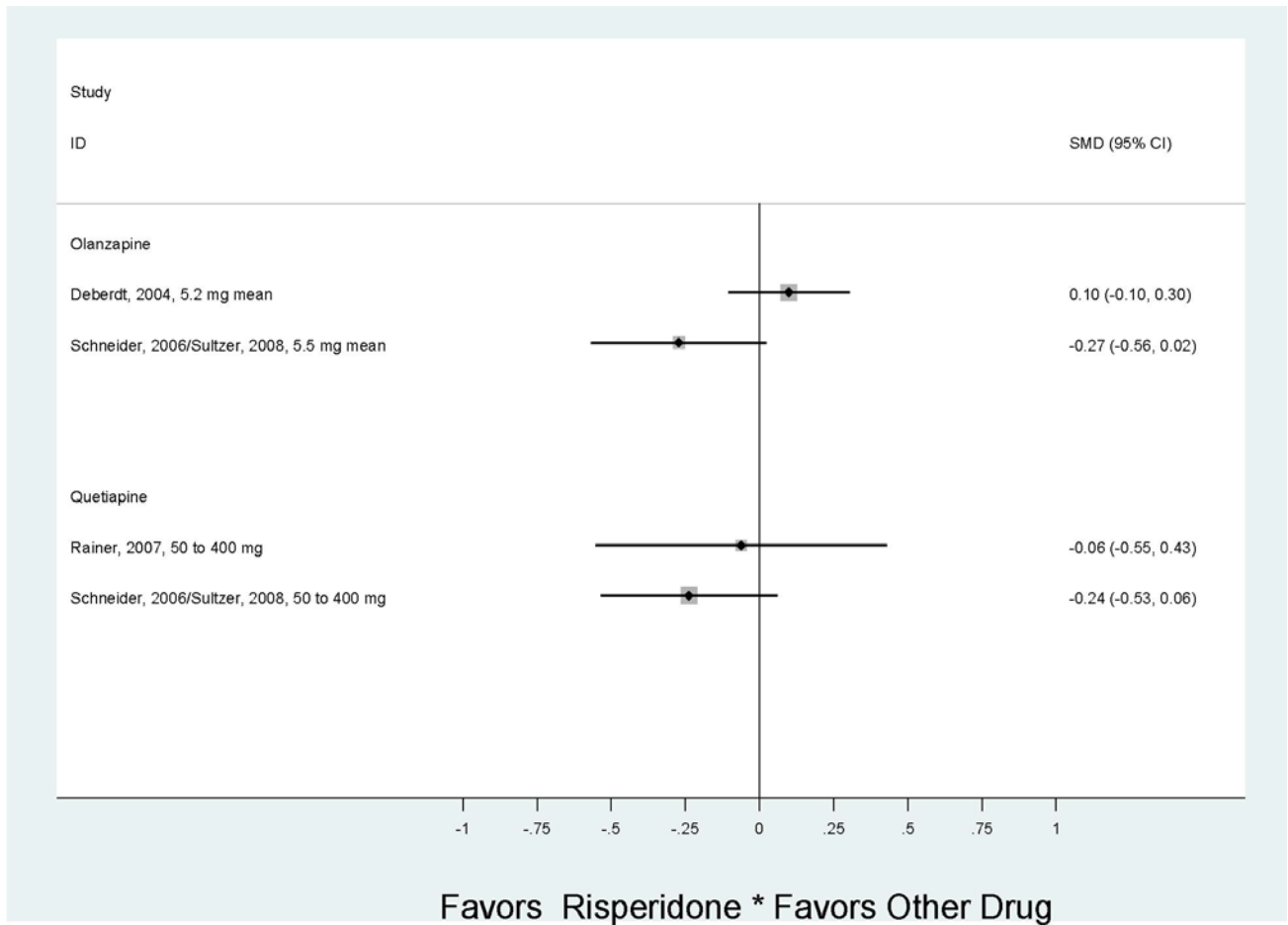


Figure 10. Head-to-head studies: olanzapine or quetiapine versus risperidone—psychosis

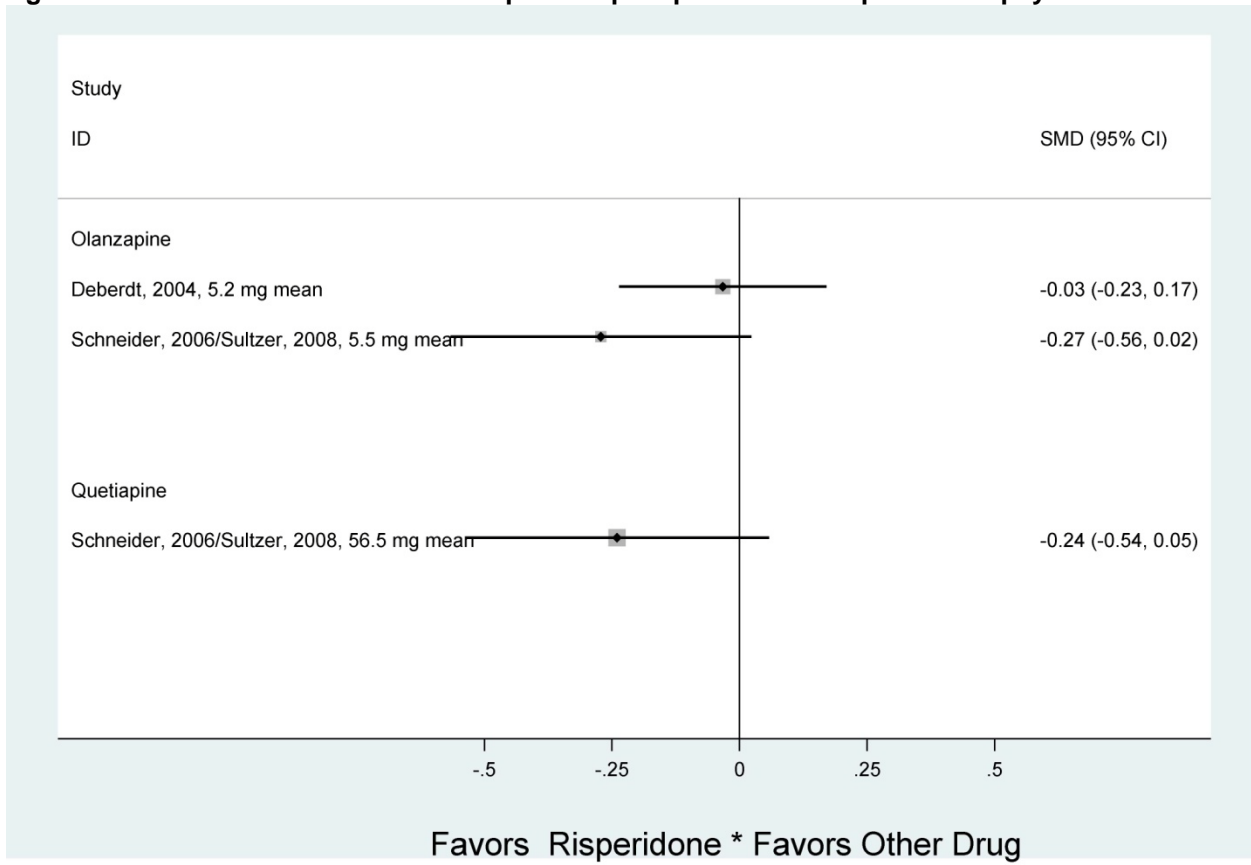
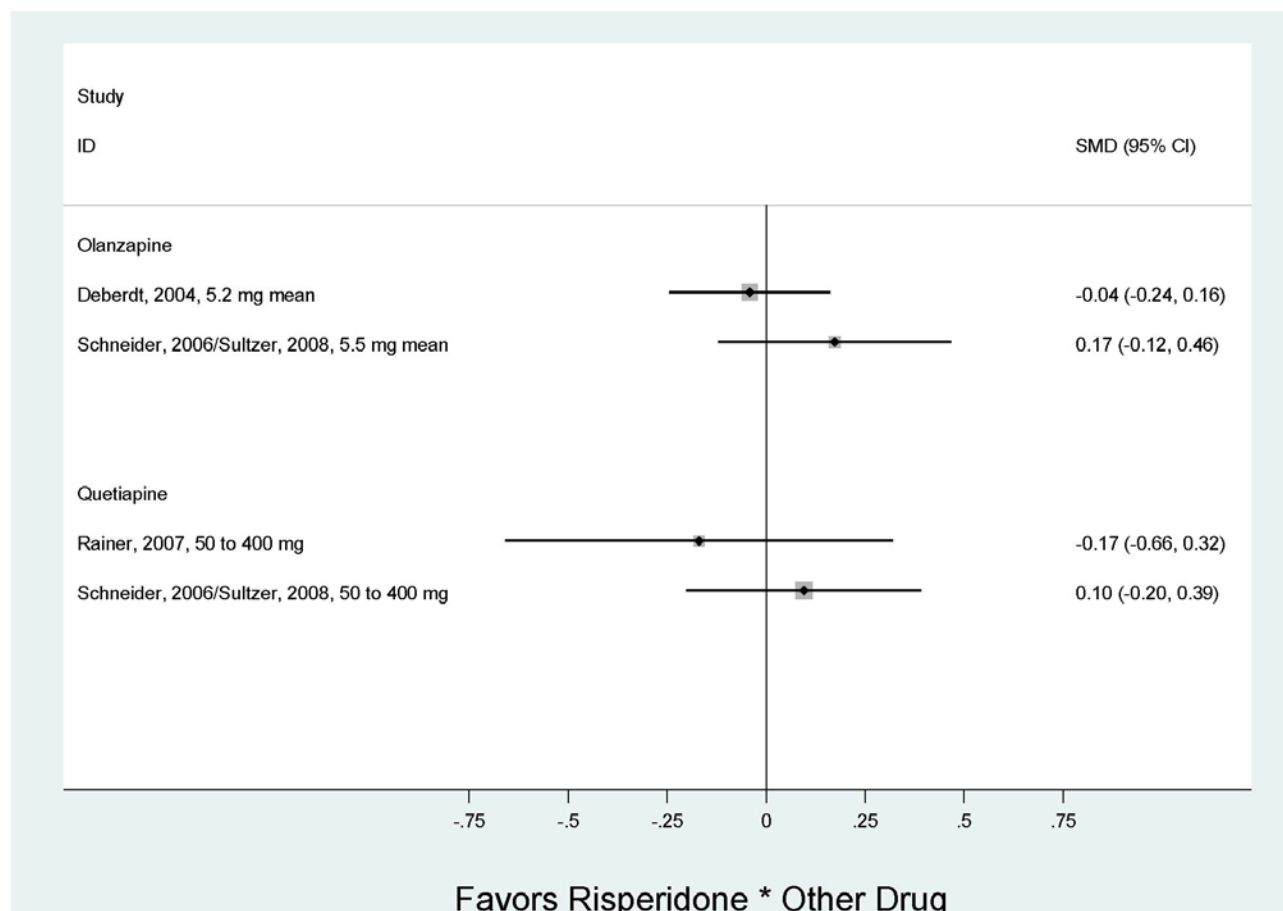


Figure 11. Dementia head-to-head studies: olanzapine or quetiapine versus risperidone—agitation



Depression. This section focuses on MDD; we excluded other types of depression, including bipolar depression or depression with psychotic features. For MDD, our 2006 CER reported that atypicals were not superior to placebo as augmentation to SSRIs at 8 weeks. However, in some trials they led to more rapid improvement (2 to 4 weeks). Since then, Papakostas published a meta-analysis on MDD in 2007¹⁵¹ and updated it in 2009.¹⁵² Both versions found atypicals superior to placebo in increasing response and remission rates, and found no statistical difference between the specific atypicals. Both versions included olanzapine, risperidone, and quetiapine; the most recent version added aripiprazole.

Our literature search identified 26 new studies of atypical antipsychotics as monotherapy or augmentation for MDD published since our original CER, 18 of which were not in the prior systematic reviews. Quality of trials ranged from 1 to 5 on the Jadad scale; mean score was 2.7. Sample sizes were usually large, with the mean close to 200. Followup times ranged from 4 weeks to 1 year.

The majority of the trials studied augmentation of SSRIs in treatment refractory patients: four of these were PCTs of aripiprazole,¹⁵³⁻¹⁵⁶ seven were PCTs of quetiapine,^{86,157-162} and five were PCTs of risperidone.¹⁶³⁻¹⁶⁷ One quetiapine PCT augmented treatment with cognitive behavioral therapy (CBT).¹⁵⁸ The results of this trial were suggestive of an added benefit of quetiapine over placebo. However, it was not considered for further analysis as it was deemed to be insufficiently clinically similar to the other studies. There were also six PCTs of quetiapine

extended release (ER) as monotherapy.¹⁶⁸⁻¹⁷³ Four other trials were not placebo controlled¹⁷⁴⁻¹⁷⁷ and thus could not be included in our pooled analyses. They will be discussed later under “active controlled trials.”

Outcomes consistently reported in the PCTs included the HAM-D total score, percent responders and percent remitted, and the MADRS total score, percent responders and percent remitted. Several trials reported both HAM-D and MADRS outcomes.^{156,161,162,165,168,169,171,172} Since the information needed to calculate an effect size for the mean MADRS and HAM-D total scores was not consistently reported, we pooled the percent responded and remitted on each scale. The patient populations were reviewed by a psychiatrist to determine level of severity, age, comorbid illness and other factors to verify that these populations were similar enough to pool. The outcomes were measured between 4 and 8 weeks, considered sufficiently clinically similar to pool. Several PCTs contained more than one treatment arm; these studies compared the effects of different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome per trial. We present the results by dosage later in the relevant section (Key Question 5).

Three trials only reported continuous outcomes, thus they were not included in pooled analyses, which used binary outcomes (e.g., percent responding or percent remitted).^{153,164,173} The first of these studied risperidone augmentation of antidepressant medication and found a significant decrease in suicidal ideation with risperidone versus placebo.¹⁶⁴ The second compared quetiapine monotherapy with placebo and found that quetiapine significantly increased the time to a depressed event, compared with placebo.¹⁷³ The third compared aripiprazole augmentation of an antidepressant to placebo augmentation. They reported a significantly greater change in MADRS total score in those receiving aripiprazole.¹⁵³ Additionally, one study did not report outcome data by arm, only overall, so was not included in pooled analysis.¹⁶³ In that study, risperidone augmentation of antidepressant therapy was reported to result in symptomatic remission in a substantial number of patients with chronic resistant depression, compared with placebo.

We conducted six meta-analyses with data from the remaining PCTs:

- Percent remitted on the HAM-D, augmentation.
- Percent responded on the HAM-D, augmentation.
- Percent remitted on the MADRS, augmentation.
- Percent responded on the MADRS, augmentation.
- Percent remitted on the MADRS, monotherapy.
- Percent responded on the MADRS, monotherapy.

HAM-D meta-analyses, augmentation trials. A person was considered remitted if their HAM-D score was less than or equal to 7 (on the HAM-D 17) or a less than or equal to 8 (on the HAM-D 24) for two consecutive visits. Two trials (from one article¹⁷⁸) from our 2006 systematic review reported percent responded and percent remitted on the HAM-D; we include them in the current meta-analyses. The eight total trials that reported the number of participants classified as remitters using the HAM-D ranged in duration from 4 to 8 weeks.^{86,157,161,165-167,178} As displayed in Table 8, the size of these trials ranged from 34 to 274 patients. Only quetiapine and risperidone had a sufficient number of studies to pool estimate of effect by drug. As displayed in Figure 12, the random effects pooled estimate of the relative risk of remitting on the HAM-D for those treated with quetiapine versus placebo was 2.76 (95% CI 1.21, 6.28), and for those taking

risperidone was 2.10 (95% CI 1.43, 3.09). This is equivalent to a NNT (number needed to treat) of five for quetiapine and eight for risperidone.

Responders on the HAM-D were identified in the same eight trials. A responder was defined as someone who had at least a 50 percent reduction in HAM-D score from randomization to followup. We were only able to calculate a pooled estimate of effect for quetiapine and risperidone, as olanzapine had only two trials. As displayed in Figure 13, the random effects pooled estimate of the relative risk of responding on the HAM-D for participants taking quetiapine compared with placebo was 2.30 (95% CI 1.35, 3.92), while for risperidone it was 1.50 (95% CI 1.20, 1.87). This is equivalent to an NNT of three for quetiapine and seven for risperidone. The overall I-squared statistic for these eight trials indicated no heterogeneity (0.0 percent). Neither Begg's nor Egger's test were statistically significant ($p=0.711, p=0.245$, respectively).

Table 8. Depression—placebo-controlled augmentation trials contributing to HAM-D meta-analysis

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Rothschild et al. 2004 ¹⁷⁸	MDD, Age \geq 18, HAM-D \geq 20	124	Placebo Olanzapine 5-20 mg/day	8 weeks	HAM-D % Remitted: Olanzapine vs Placebo – RR=1.45 (0.42, 5.07) HAM-D % Responded: Olanzapine vs Placebo – RR= 1.25 (0.68, 2.28)
Rothschild et al. 2004 ¹⁷⁸	MDD, Age \geq 18, HAM-D \geq 20	125	Placebo Olanzapine 5-20 mg/day	8 weeks	HAM-D % Remitted: Olanzapine vs Placebo – RR= 1.09 (0.40, 3.00) HAM-D % Responded: Olanzapine vs Placebo – RR= 1.14 (0.64, 2.02)
Mattingly et al. 2006 ¹⁶¹	Outpatients aged 18-65 years old, a primary diagnosis of MDD who were not psychotic, baseline HAM-D 17 \geq 20 following a \geq 6 weeks SSRI or SNRI treatment, HAM-D item I score \geq 2 had failed \geq 1 r-week trial of clinically appropriate dose of another antidepressant	40	Placebo Quetiapine 200-400 mg/day	8 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 2.83 (0.73, 10.98) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.12 (0.89, 5.05)
McIntyre et al. 2007 ⁸⁶	18-65, MDD, HAM-D 17 \geq 18, CGI-S \geq 4, HAM-A \geq 14, treated with single SSRI/venlafaxine at a therapeutic dose \geq 6 weeks	58	Placebo Quetiapine 50-600 mg/day	8 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 1.78 (0.53, 5.97) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.00 (0.76, 5.26)
Zheng et al. 2007 ¹⁵⁷	Diagnosed with MDD without psychotic symptoms, HAM-D score \geq 18, BPRS item 4 score \leq 4, item 11 score \leq 3, had been treated unsuccessfully with \geq 2 different types of antidepressants for \geq 6 weeks	NR	Placebo Quetiapine 50-200 mg/day	4 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 8.44 (1.17, 60.94) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.90 (1.13, 7.47)

Table 8. Depression—placebo-controlled augmentation trials contributing to HAM-D meta-analysis (continued)

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Gharabawi et al. 2006 ¹⁶⁷	Adult outpatients with DSM-IV MDD, had an incomplete response to \geq 8 weeks of antidepressant treatment	274	Placebo Risperidone 0.25-2 mg/day	6 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 2.03 (1.10, 3.75) HAM-D % Responded: Risperidone vs Placebo – RR = 1.44 (1.03, 2.01)
Keitner et al. 2009 ¹⁶⁵	Depressed, failed current antidepressant trial. MADRS \geq 15, 18-65	97	Placebo Risperidone 0.5-3 mg/day	4 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 1.95 (0.88, 4.33) HAM-D % Responded: Risperidone vs Placebo – RR = 1.49 (0.83, 2.68)
Mahmoud et al. 2007 ¹⁶⁶	18-65, antidepressant monotherapy \geq 4 weeks, MDD, CGI-S \geq 4	274	Placebo Risperidone 0.25-2 mg/day	6 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 2.29 (1.22, 4.30) HAM-D % Responded: Risperidone vs Placebo – RR = 1.57 (1.20, 1.87)

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; RR = relative risk; SSRI = selective serotonin reuptake inhibitor

Figure 12. Depression—HAM-D % remitted, augmentation

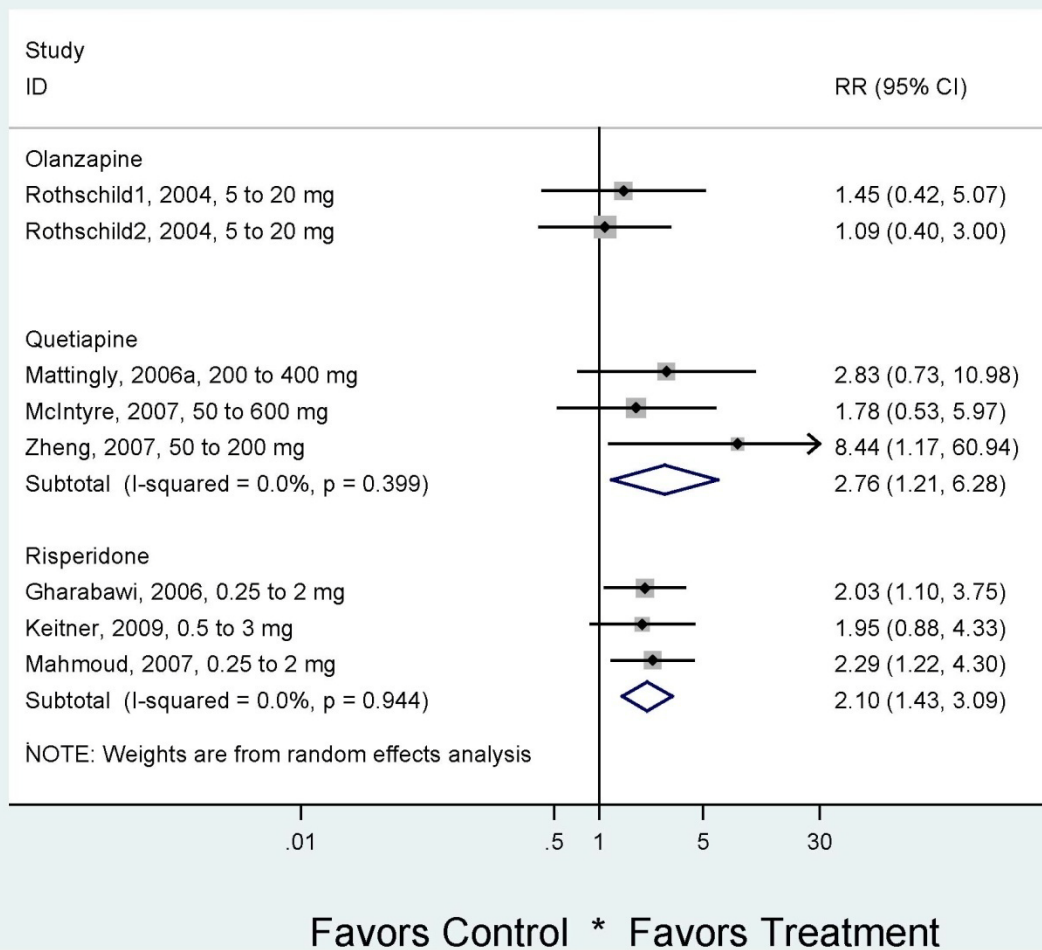
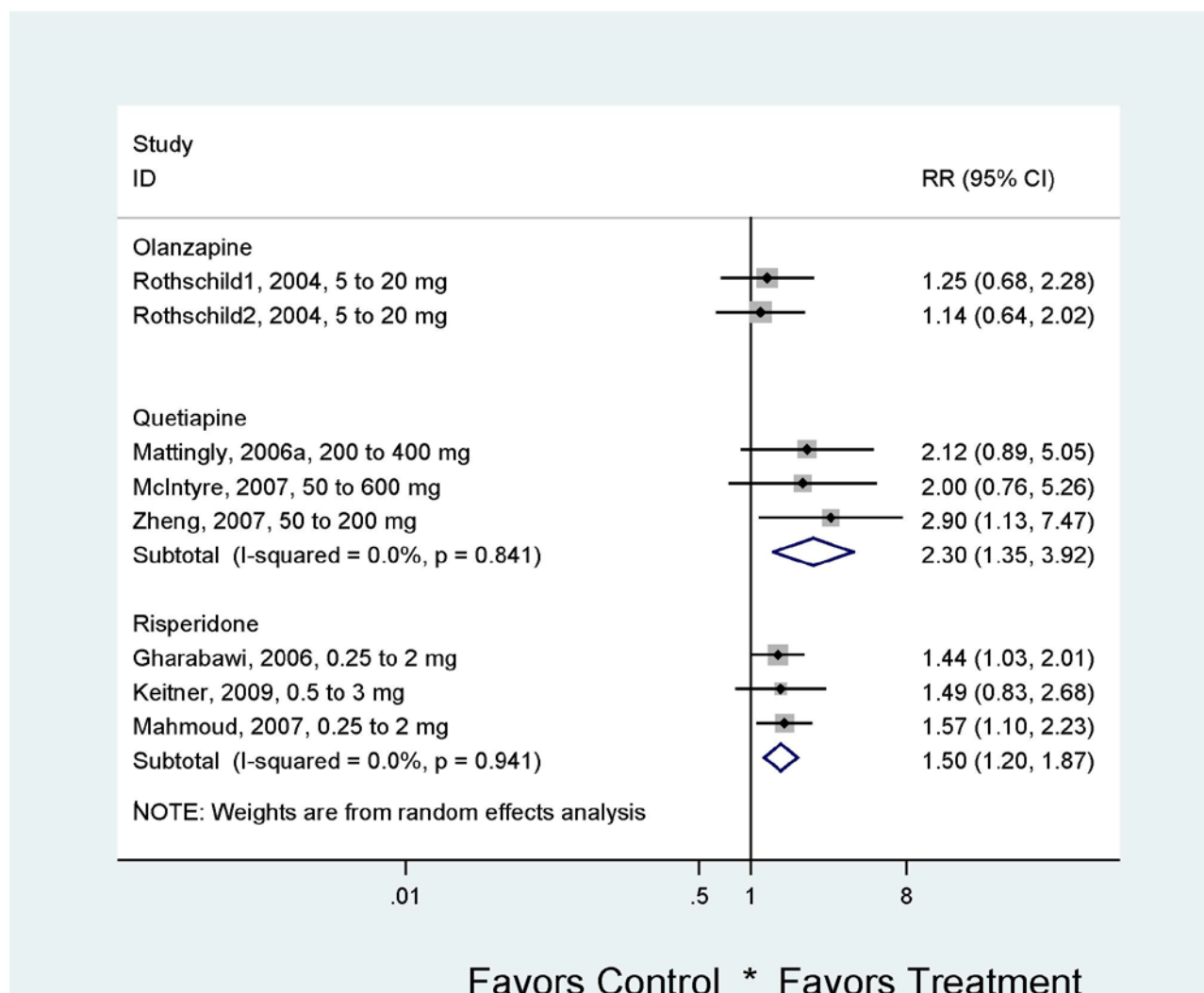


Figure 13. Depression—HAM-D % responded, augmentation



MADRS meta-analyses, augmentation trials. On the MADRS scale, the definition of a remitted participant differed slightly between trials. A person was considered remitted if their MADRS score was from 8 to 10, depending on the study. The seven trials that reported the number of participants classified as remitters ranged in duration from 4 to 8 weeks.^{154-156,159,160,162,165}

As displayed in Table 9, the size of these trials ranged from 97 to 493. Only aripiprazole and quetiapine had a sufficient number of studies to report the pooled estimate of effect per drug. As displayed in Figure 14, the random effects pooled estimate of the relative risk of remitting on the MADRS for those treated with aripiprazole versus placebo was 1.57 (95% CI 1.24, 2.00); for those taking quetiapine it was 1.24 (95% CI 0.82, 1.88). The I-squared statistics for these two analyses were 0 and 82.8, respectively. Begg’s test approached significance (p = .072) and Egger’s test was significant (p = .018) indicating possible publication bias.

Responders on the MADRS were identified in all but one trial¹⁶⁰ that reported remitters. A responder was defined as someone who had at least a 50 percent reduction in MADRS score from randomization to followup. We were able to calculate a pooled estimate of effect for aripiprazole, which had three trials. Quetiapine was included in two trials, while risperidone was

included in only one. As displayed in Figure 15, the random effects pooled estimate of the relative risk of responding on the MADRS for those participants taking aripiprazole compared with placebo was 1.66 (95% CI 1.37, 2.01); for an NNT of seven. The I-squared statistic for this analysis was 0.0. Begg's test was not significant ($p = 0.260$), while Egger's test approached significance ($p = .069$).

Table 9. Depression—placebo-controlled augmentation trials contributing to MADRS meta-analysis

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Berman et al. 2007 ¹⁵⁵	Diagnosed MDD ≥ 8 weeks, inadequate response to antidepressant, ($< 50\%$ reduction in depressive symptoms severity), HAM-D-17 ≥ 18	362	Placebo Aripiprazole 2-20 mg/day	6 weeks	MADRS % Remitted: Aripiprazole vs Placebo - RR = 1.65 (1.08 , 2.53) MADRS % Responded: Aripiprazole vs Placebo - RR = 1.41 (1.01 , 1.98)
Berman et al. 2009 ¹⁵⁶	18-65 years old, diagnosed major depressive episode ≥ 8 weeks, inadequate response to previous antidepressants	349	Placebo Aripiprazole 2-20 mg/day	8 weeks	MADRS %: Aripiprazole vs Placebo - RR = 1.43 (0.96 , 2.12) MADRS % Responded: Aripiprazole vs Placebo - RR = 1.75 (1.30 , 2.35)
Marcus et al. 2008 ¹⁵⁴	18-65 years old, major depressive episode ≥ 8 weeks, inadequate response to previous antidepressants	382	Placebo Aripiprazole 2-20 mg/day	6 weeks	MADRS % Remitted: Aripiprazole vs Placebo - RR = 1.67 (1.10 , 2.54) MADRS % Responded: Aripiprazole vs Placebo - RR = 1.86 (1.37 , 2.01)
Bauer et al. 2009 ¹⁶²	18-65 yrs old, diagnosed MDD, outpatients, HAM-D total score ≥ 20 . HAM-D item I score ≥ 2 , inadequate response during current episode to antidepressants.	493	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.42 (1.03 , 1.94) MADRS % Responded: Quetiapine vs Placebo - RR = 1.22 (1.01 , 1.48)
El-Khalili, 2010 ¹⁵⁹	18-65 years old, DSM-IV diagnosis of MDD, confirmed by MINI, have been on treatment with an antidepressant ≥ 6 weeks, HAM-D total score ≥ 20 , HAM-D item 1 score ≥ 2 at both enrollment and randomization.	446	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.58 (1.15 , 2.19) MADRS % Responded: Quetiapine vs Placebo - RR = 1.20 (0.98 , 1.47)
Garakani et al. 2008 ¹⁶⁰	18-65 years old, diagnosis of unipolar major depression without psychotic features, MADRS score > 15 at both screen and baseline	114	Placebo 25-100 mg/day Quetiapine 25-100 mg/day	8 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 0.87 (0.67 , 1.13)
Keitner et al. 2009 ¹⁶⁵	Depressed, failed current antidepressant trial. MADRS ≥ 15 , 18-65	97	Placebo Risperidone 0.5-3 mg/day	4 weeks	MADRS % Remitted: Risperidone vs Placebo - RR = 2.13 (1.11 , 4.08) MADRS % Responded: Risperidone vs Placebo - RR = 1.65 (0.97 , 2.80)

HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; RR = relative risk

Figure 14. Depression—MADRS % remitted, augmentation

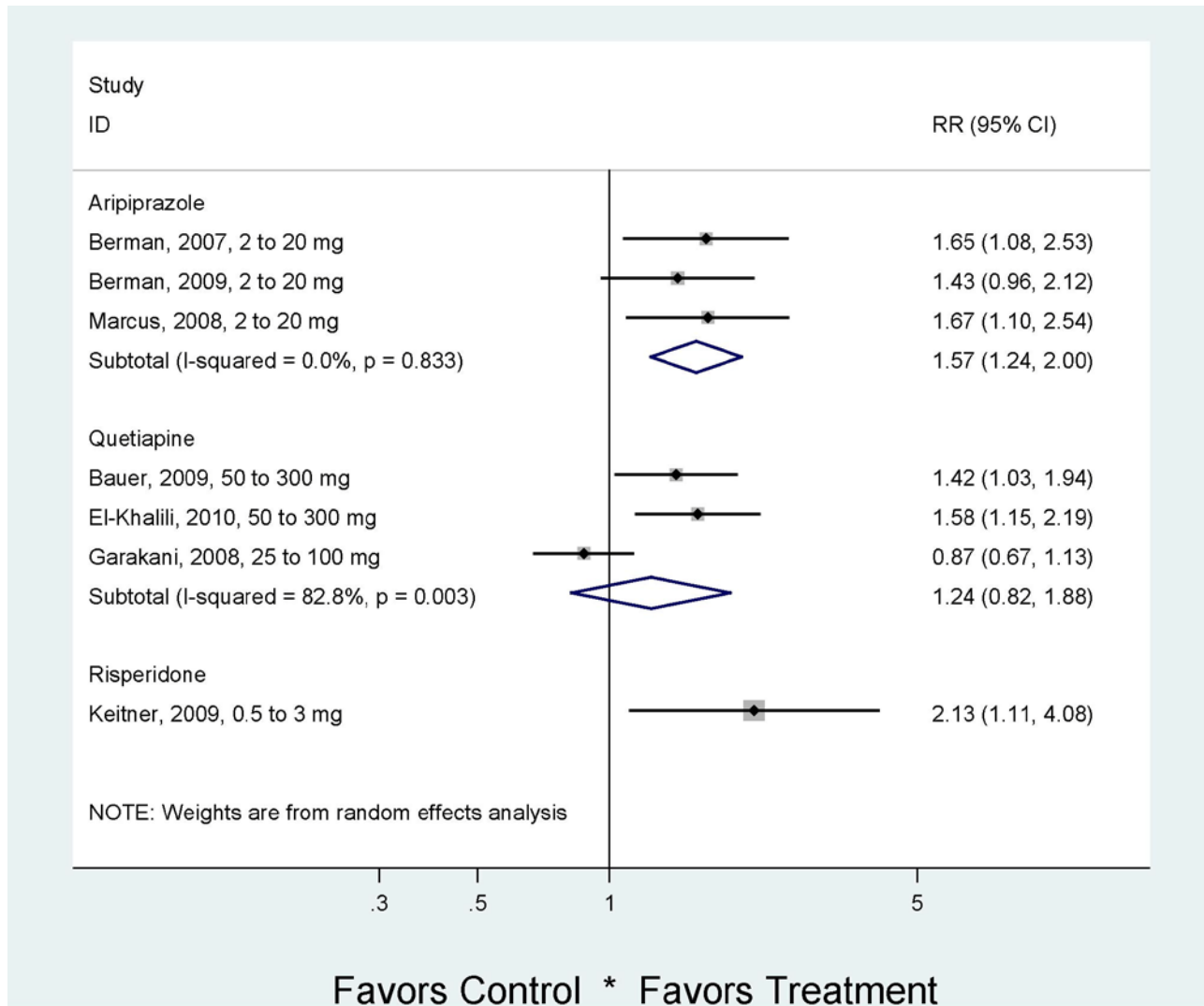
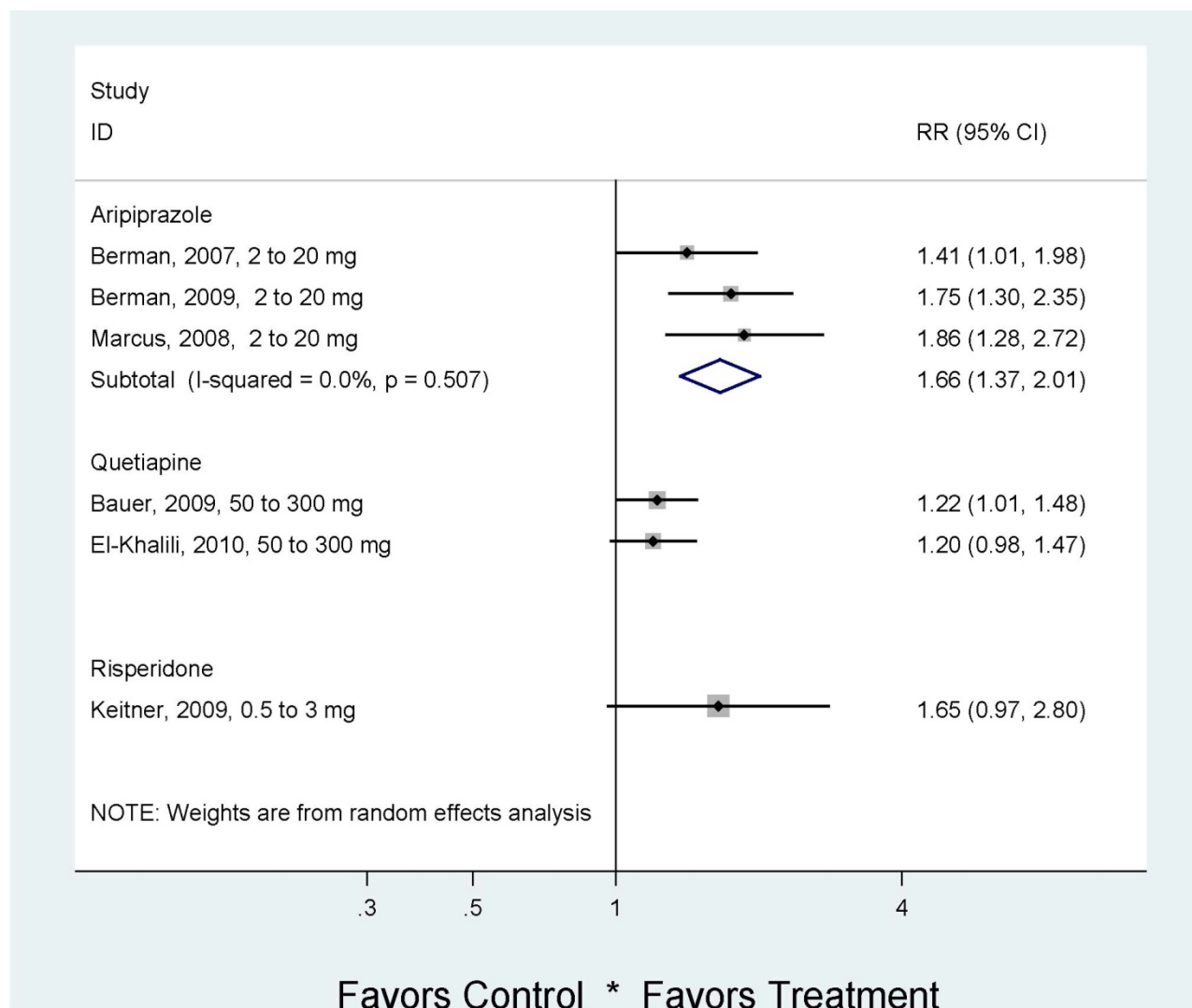


Figure 15. Depression—MADRS % responded, augmentation



MADRS meta-analyses, monotherapy trials. The five monotherapy trials for MDD ranged in length from 6 to 9 weeks.¹⁶⁸⁻¹⁷² The number of enrollees ranged from 310 to 723; all studied quetiapine and reported both on both remitters and responders. Details of the studies are displayed in Table 10. As displayed in Figure 16, the random effects pooled estimate of remitting on the MADRS for those treated with quetiapine versus placebo was 1.43 (95% CI 1.07, 1.91). Begg's and Egger's tests were not statistically significant ($p = 0.86$, $p = .142$, respectively). Figure 17 presents the results using percent of patients responding. Quetiapine patients were significantly more likely to respond (OR 1.49, 95 percent CI 1.23, 1.81) than placebo patients. Begg's and Egger's test were both statistically significant ($p = .027$ each) indicating the possibility of publication bias. The I-squared statistic for each analysis was 70.7 percent and 72 percent respectively.

Table 10. Placebo-controlled monotherapy trials contributing to MADRS meta-analyses

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
AstraZeneca 2007 ¹⁶⁸	18-65 years old, DSM-IV diagnosis of MDD, HAM-D score ≥ 22 , HAM-D item 1 score ≥ 2	471	Placebo Quetiapine 50-300 mg/day Escitalopram 10-20 mg/day	9 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.01 (0.75 , 1.37) MADRS % Responded: Quetiapine vs Placebo - RR = 1.18 (0.97 , 1.45)
AstraZeneca 2008 ¹⁶⁹	Age ≥ 66 , DSM-IV diagnosis of MDD confirmed by MINI. HAM-D total score ≥ 22 , HAM-D item 1 score ≥ 2 at both enrollment and randomization.	338	Placebo 50-300 mg/day Quetiapine 50-300 mg/day	9 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 2.48 (1.70 , 3.62) MADRS % Responded: Quetiapine vs Placebo - RR = 2.11 (1.63 , 2.71)
Bortnick, 2011 ¹⁷⁰	18 -65 years old, MDD confirmed by the MINI and DSM-IV, have a HAM-D ≥ 22 , HAM-D item1 score ≥ 2 at both enrollment and randomization	310	Placebo 50-300 mg/day Quetiapine 50-300 mg/day	8 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.39 (0.97 , 1.98) MADRS % Responded: Quetiapine vs Placebo - RR = 1.29 (1.05 , 1.59)
Cutler et al. 2009 ¹⁷¹	18-65 years old, diagnosed MDD, HAM-D total score ≥ 22 , HAM-D item 1 score ≥ 2 at enrollment and randomization	612	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day Duloxetine 60 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.43 (1.03 , 2.06) MADRS % Responded: Quetiapine vs Placebo - RR = 1.51 (1.20 , 1.91)
Weisler et al. 2009 ¹⁷²	18-65, output, MDD, HAM-D item 17 ≥ 22 , HAM-D item 1 ≥ 2	723	Placebo Quetiapine 50 mg/day Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.27 (0.89 , 1.82) MADRS % Responded: Quetiapine vs Placebo - RR = 1.58 (1.24 , 2.02)

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder

Figure 16. Depression—MADRS % remitted, monotherapy

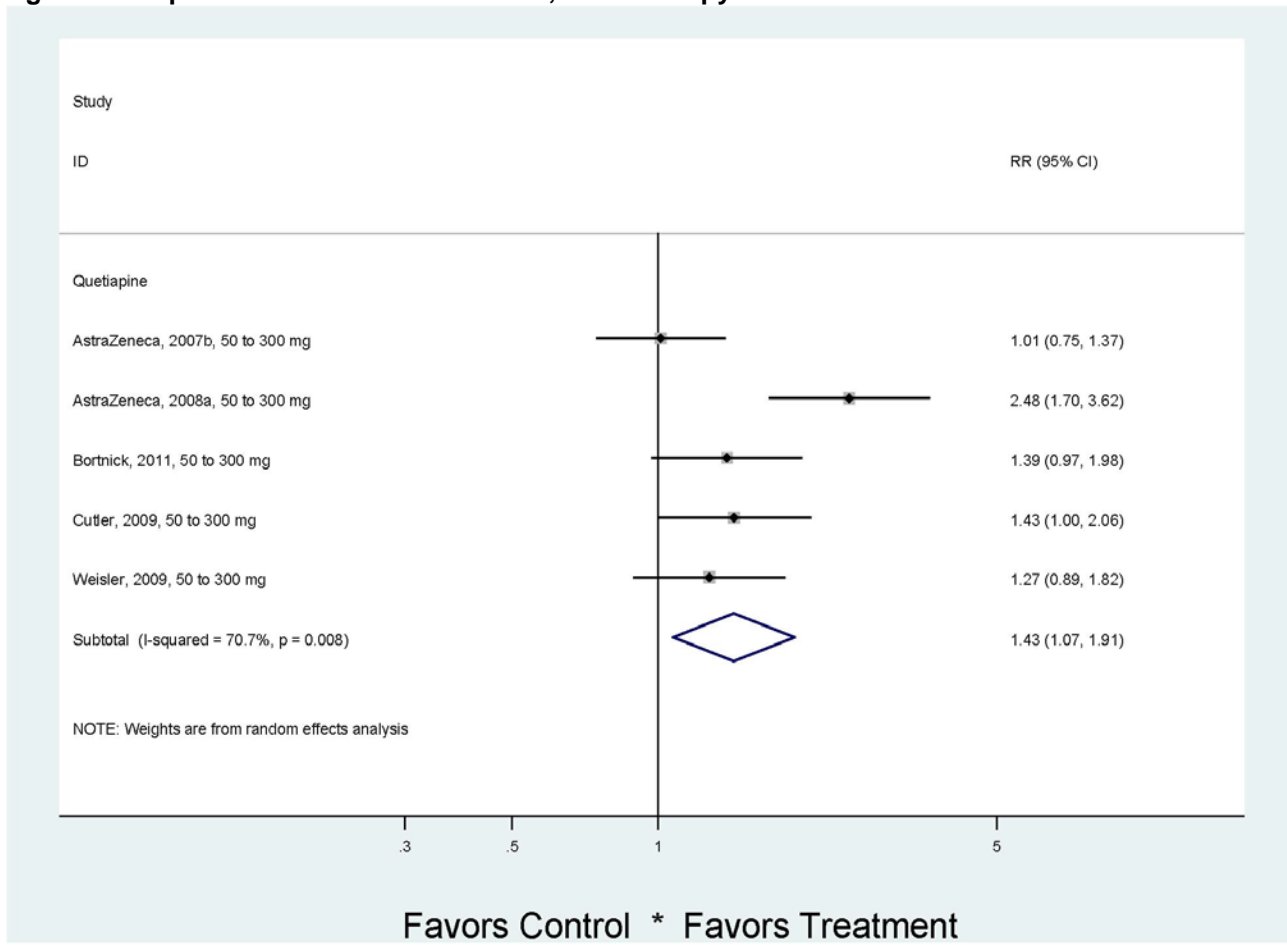
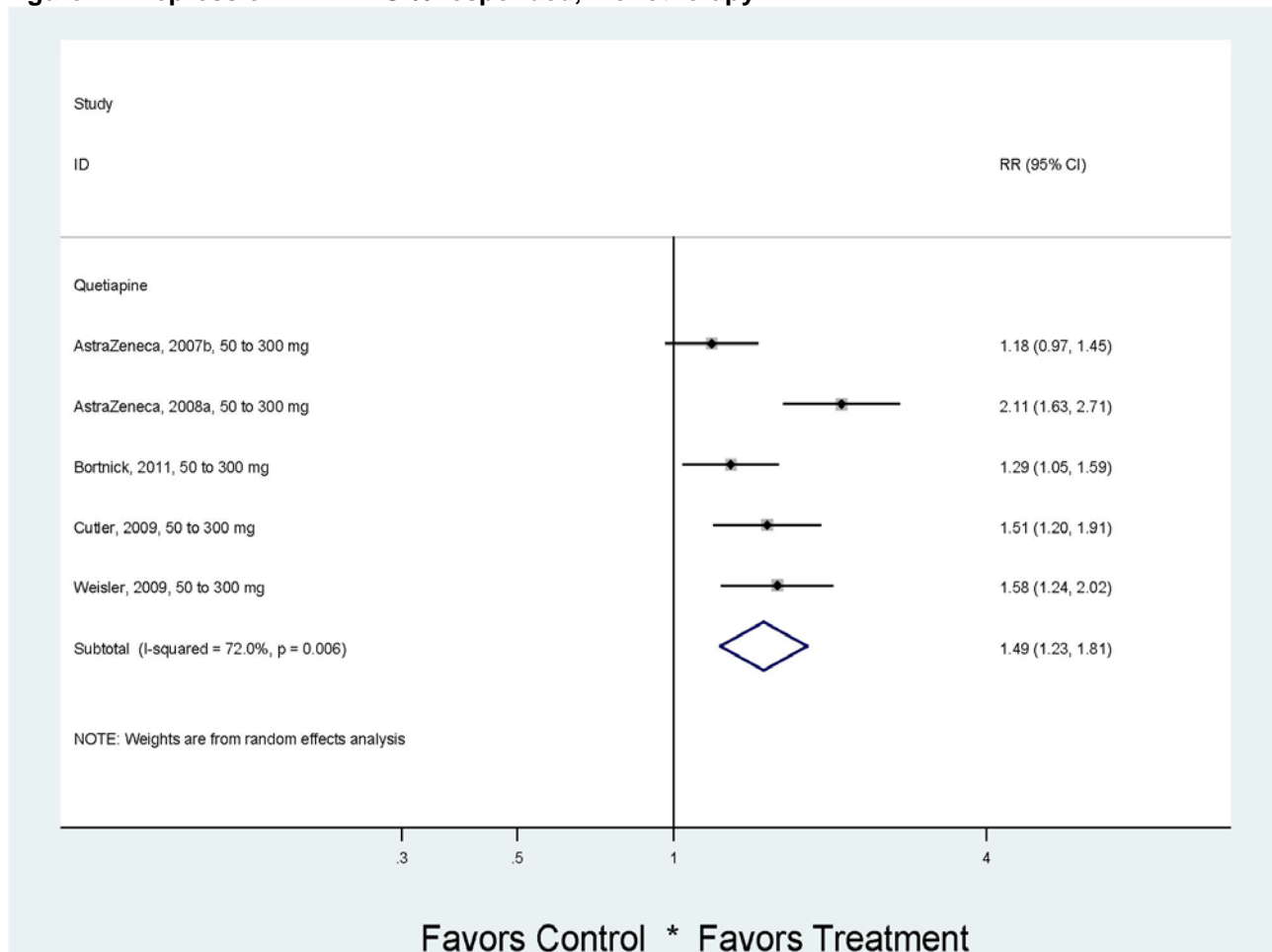


Figure 17. Depression—MADRS % responded, monotherapy



Active Controlled Trials. There were four active controlled trials of atypicals for the treatment of MDD. One study included two parallel 8-week double-blind trials comparing treatment with a combination of olanzapine and fluoxetine versus olanzapine alone versus fluoxetine alone.¹⁷⁴ The authors report that the pooled results of the two studies found significant differences in mean change of MADRS scores for the olanzapine/fluoxetine combination, compared with either fluoxetine or olanzapine alone. Another trial evaluated quetiapine versus lithium for 56 days and found greater improvement with quetiapine, according to HAM-D, MADRS, and Wildlocher Psychomotor Retardation Scales scores.¹⁷⁵ An 8-week trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone.¹⁷⁶ This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAM-D 17, CGI-I, or HAM-A scores. The final non –placebo-controlled trial compared quetiapine as augmentation of paroxetine or venlafaxine to venlafaxine or paroxetine alone.¹⁷⁷ This 12-week trial found an improvement in HAMD-17 scores for all groups, with the quetiapine- paroxetine combination showing the greatest improvement, followed by the quetiapine-venlafaxine combination, then paroxetine only and finally venlafaxine only.

Head-to-Head Trials. No trials comparing specific atypical antipsychotics for MDD were found.

Eating Disorder. This off-label use was not included in our 2006 systematic review. We found one systematic review on this topic; it included RCTs, observational studies, and case reports.¹⁷⁹ The review found evidence of improvement in psychological symptoms, but not in weight gain. Our literature search identified five trials that assessed olanzapine for this use¹⁸⁰⁻¹⁸⁴ and one of quetiapine.¹⁸⁵ Mean quality score was 2.0 on the Jadad scale. Trials ranged in length from 2 to 3 months. Sample sizes were small, with 15 to 45 participants, per trial. All of the RCTs were placebo controlled except for one small head-to-head trial that compared olanzapine to a conventional antipsychotic, chlorpromazine,¹⁸¹ in which the olanzapine group had a significant reduction in anorexic rumination. This trial was excluded from quantitative analysis, which included only placebo comparisons.

Four of five remaining studies reported BMI at times between 1 and 13 weeks. One study that only reported weight gain per week was excluded from further analysis.¹⁸⁴ In that study, there were no differences in weight gain by whether they were treated with olanzapine.

The sample size of the four remaining trials ranged from 20 to 34. These trials were deemed clinically similar to justify meta-analysis at 1 and 3 months; their results are displayed in Table 11.^{180,182,183,185} (BMI is measured such that the desired effect is an increase.)

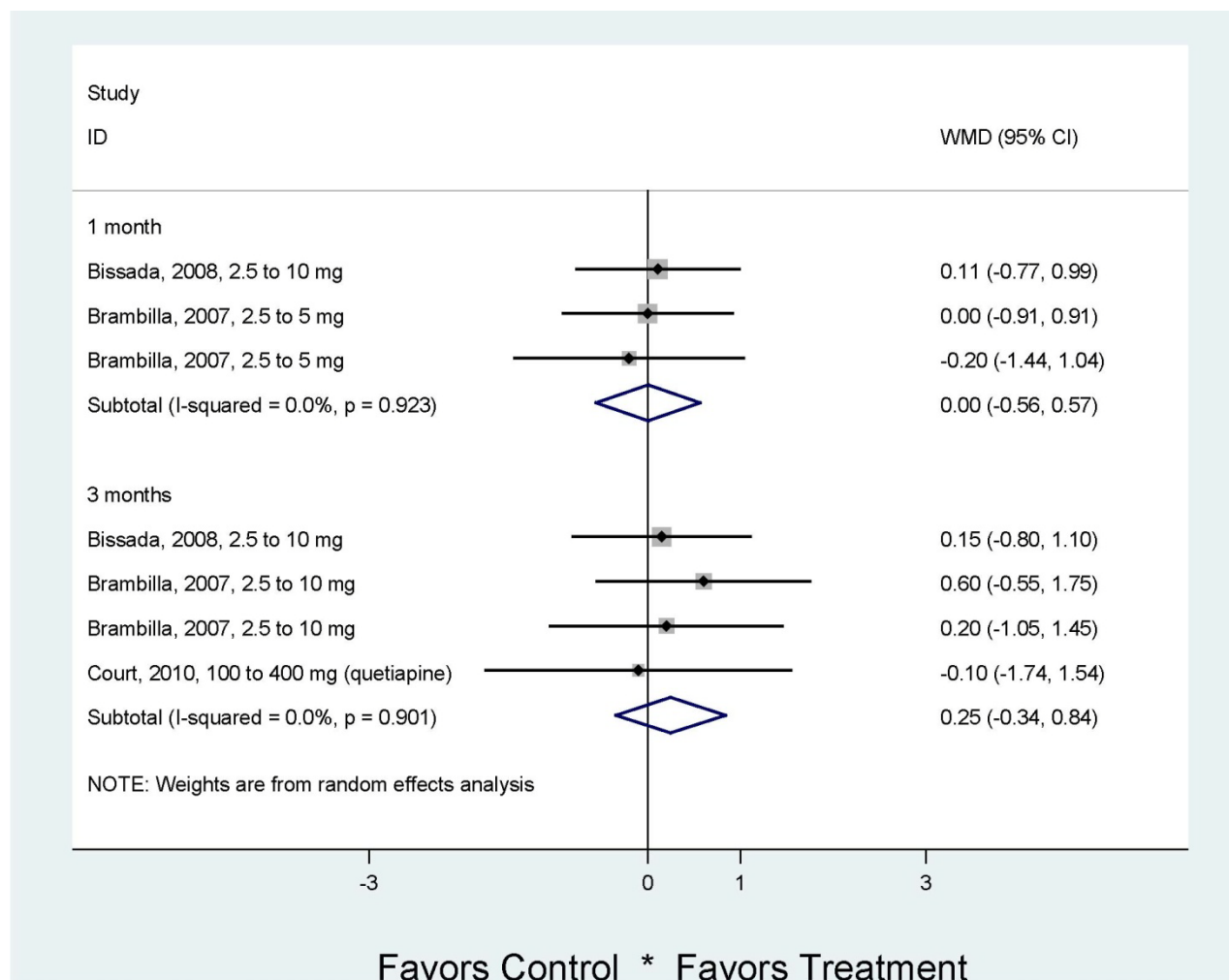
The random effects pooled weighted mean difference in BMI from baseline to 1 month of treatment with olanzapine was .004 (95% CI -0.56, 0.57). At 3 months the random effects pooled estimate was 0.25 (95% CI -0.34, 0.84) (Figure 18). The I-squared statistic for each time point indicated low heterogeneity. Neither Begg's or Egger's test for publication bias were statistically significant at either time point (1 month $p=0.30$, $p=0.21$ respectively; 3 months $p=0.73$, $p=0.68$ respectively).

Table 11. Eating disorder—PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Bissada et al. 2008 ¹⁸⁰	DSM-IV criteria for anorexia nervosa (restricting or binge / purge subtype) including a body index <= 17.5 kg/m ²	34	Placebo Olanzapine 2.5-10 mg/day	10 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo - WMD = 0.11 (-0.77 , 0.99) Change in BMI at 12 weeks: Olanzapine vs. Placebo - WMD = 0.15 (-0.80 , 1.10)
Brambilla et al. 2007 ¹⁸²	Anorexia nervosa per DSM-IV, restricted or binge-purging type	30	Placebo Olanzapine 2.5-5 mg/day	12 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo - WMD = -0.00 (-0.91 , 0.91) Change in BMI at 12 weeks: Olanzapine vs. Placebo - WMD = 0.60 (-0.55 , 1.75)
Brambilla et al. 2007 ¹⁸³	Anorexia nervosa according to DSM-IV	20	Placebo Olanzapine 2.5-5 mg	12 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo - WMD = -0.20 (-1.44 , 1.04) Change in BMI at 12 weeks: Olanzapine vs. Placebo - WMD = 0.20 (-1.05 , 1.45)
Court, 2010 ¹⁸⁵	Anorexia nervosa per DSM-IV	27	Placebo Quetiapine 100-400mg/day	12 weeks	Change in BMI at 12 weeks: Quetiapine vs. Placebo - WMD = -0.10 (-1.74 , 1.54)

BMI = body mass index; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; WMD = weighted mean difference

Figure 18. Eating disorders—BMI



Active Controlled Trials. There were no active controlled trials of atypicals for eating disorders.

Head-to-Head Trials. There were no head-to-head trials of atypicals for eating disorder.

Insomnia. This off-label use was not included in our 2006 CER. We found no meta-analyses or systematic reviews on the use of atypical antipsychotics for insomnia treatment. We found only one small RCT conducted in Thailand. Although the quetiapine group increased total sleep time by 125 minutes, compared with an increase of 72 minutes in the placebo group, the difference was not statistically significant, due to small sample size (N=13). Because of the paucity of information on this use, we describe six observational studies identified in our literature search; two utilized olanzapine while four utilized quetiapine. Study characteristics are displayed in Table 12 and 13.

One olanzapine study treated 12 patients with insomnia related to major depressive disorder for three weeks. These patients experienced improvements in sleep efficiency, subjective sleep quality and slow wave sleep.¹⁸⁶ The other olanzapine study included case reports of nine patients

with different sleep disorders followed for up to 3 years. Eight patients experienced improvements in sleep including sleep latency, total sleep time, decreased nightmares and unspecified improvements.¹⁸⁷ In both studies, the dosages ranged from 2.5mg to 10mg each night and measurements were done both subjectively and per polysomnogram.

Quetiapine was used to treat insomnia of various causes including: primary insomnia,¹⁸⁸ insomnia of drug withdrawal,¹⁸⁹ tamoxifen-related insomnia¹⁹⁰ and insomnia of Parkinson's disease.¹⁹¹ The dosages ranged from 12.5mg to 225mg each night, and the patients were treated from 6 weeks to 3 months. Sleep was measured both objectively using a polysomnogram¹⁸⁸ and subjectively using the Pittsburgh Sleep Quality Inventory,^{188,191} the Italian version of the Insomnia Severity Index Scale,¹⁹⁰ Speigal Sleep Questionnaire,¹⁸⁹ and the Epworth Sleep Scale.¹⁹¹ All studies showed improvements in sleep including total sleep time, sleep efficiency,¹⁸⁸ overall quality of sleep,¹⁸⁹ all aspects of sleep,¹⁹¹ and unspecified improvements.¹⁹⁰ Of note, one study did not show an improvement in sleep latency¹⁸⁸ while two others did.^{189,191}

Table 12. Atypical antipsychotics for insomnia, observational studies—olanzapine

Study/Type	Insomnia Type	N	Dosage/Duration	Measures	Effects/AEs
Estivill, 2004 ¹⁸⁷	Unspecified	9	2.5mg-10mg/	Polysomnogram	Improved sleep latency (3), feeling of good sleep (2), total sleep time (3). Decreased nightmares (1). Unspecified improvement (3). No improvement (1)
Case series			Up to 3 years	(8/9)	
Sharpley, 2005 ¹⁸⁶	Insomnia in major depressive disorder	12	2.5-10mg (mean 4.8mg)/	Polysomnogram	Improved sleep efficiency, subjective sleep quality, slow wave sleep
Open label	unresponsive to SSRI treatment		3 weeks		

AE = adverse effect; SSRI = selective serotonin reuptake inhibitor

Table 13. Atypical antipsychotics for insomnia, observational studies—quetiapine

Study/Type	Insomnia Type	N	Dosage/Duration	Measures	Effects/AEs
Juri, 2005 ¹⁹¹	Insomnia of Parkinson's Disease	14	12.5-50mg (mean 31.9mg)/	Pittsburgh Sleep Quality Inventory , Epworth Sleep Scale	All aspects of sleep improved, greatest improvement in sleep onset, daytime sleepiness improved
Case series			Up to 3 months		
Pasquini, 2009 ¹⁹⁰	Tamoxifen-related insomnia	6	25-100mg/	Insomnia Severity Index- Italian version	"prompt improvement"
Case series			6 weeks		
Teran, 2008 ¹⁸⁹	Insomnia as main symptom of withdrawal syndrome	52	25-225mg (mean 50mg)/	Speigal Sleep Questionnaire	"greatest improvements in overall quality of sleep and time to falling asleep"
Chart review			Up to 60 days		
Wiegand, 2008 ¹⁸⁸	Primary insomnia	18	25-75mg/	Polysomnogram, PSQI	Improved total sleep time and sleep efficiency
Open label pilot study			6 weeks		

AE = adverse effect

Obsessive-Compulsive Disorder. Our 2006 CER concluded that atypicals have a clinically meaningful benefit when used as augmentation therapy in patients with OCD. That report included a meta-analysis we conducted using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as outcome; both quetiapine and risperidone augmentation increased the odds of response, when compared with augmentation with placebo. (At that time, there were too few trials of olanzapine to permit pooling.) Three other meta-analyses assessing atypical

antipsychotics as augmentation for treatment-resistant OCD patients were published around the time of our first evidence report. Two^{192,193} included trials of risperidone, quetiapine, and olanzapine. They both found the atypicals have efficacy in increasing the number of responders on the Y-BOCS. Risperidone was statistically significant, while quetiapine and olanzapine had a trend toward efficacy that was not statistically significant. The other meta-analysis included only quetiapine; the authors pooled two trials and found the drug superior to placebo, as measured by changed in total Y-BOCS score.¹⁹⁴

Our literature search identified eight reports of trials published after our 2006 CER.¹⁹⁵⁻²⁰² Trials were relatively small compared with trials for dementia, anxiety, and depression; sample sizes ranged from 18 to 66. Four were controlled trials of an atypical antipsychotic versus another drug, with no placebo group. These will be discussed below in the section on active controlled and head to head trials.

The other five trials reported on PCTs of augmentation. These trials ranged in duration from 8 to 12 weeks and measured the change in Y-BOCS as the primary outcome measure. Three evaluated the treatment of OCD with quetiapine plus citalopram or placebo plus citalopram,^{199,201,202} in patients with OCD who were currently not taking any pharmacotherapy. All three of these studies are related and may in fact be from one trial: they are from the same group of authors using nearly identical protocols, and two studies report on 76 patients while one study reports on 82 patients. These papers report that in treatment-naïve patients quetiapine augmentation was superior to placebo according to improvement in both Y-BOCS and CGI-I scores. The final two studies evaluated quetiapine plus serotonin reuptake inhibitor (SRI) or placebo plus SRI treatment.^{196,197} One of these reported duplicate data to an already-included study²⁰³ and was therefore excluded from our pooled analysis.

These final two new RCTs that evaluated quetiapine augmentation versus placebo^{196,197} along with four RCTs identified in our original report that evaluated the same treatment,²⁰⁴⁻²⁰⁶ two from the original report that evaluated olanzapine augmentation versus placebo,^{207,208} and three from the original report that assessed risperidone augmentation versus placebo²⁰⁹⁻²¹¹ were deemed sufficiently clinically similar to justify meta-analysis. These trials are displayed in Table 14.

These 10 trials used the Y-BOCS as the primary outcome, classifying “responders” as those achieving a 25 to 35 percent improvement on the Y-BOCS total score. The sample sizes ranged from 16 to 45. The outcome “responders” on the Y-BOCS was measured at 6 to 12 weeks. A few PCTs^{204,207,210} reported very wide confidence intervals; these trials were published earlier (2002 to 2004) than the rest.

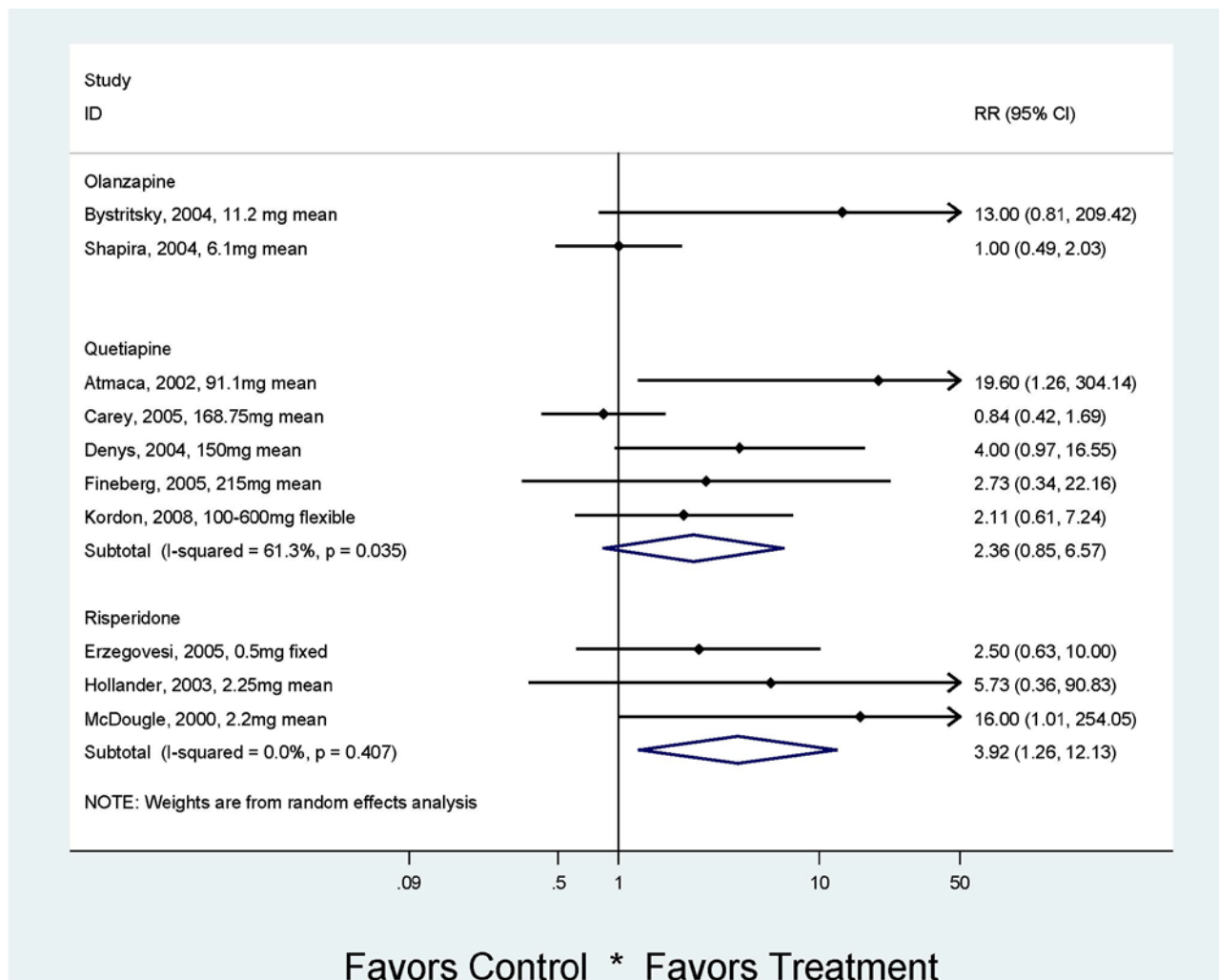
The meta-analysis results are displayed in Figure 19. There were enough studies to calculate a pooled estimate of relative risk for risperidone and quetiapine. The relative risk of “responding” on the Y-BOCS for those in the quetiapine augmentation arm versus those in the placebo arm was 2.36 (95% CI 0.85, 6.57). The relative risk of “responding” on the Y-BOCS for those in the risperidone augmentation arm was 3.92 (95% CI 1.27, 12.13). This results in an NNT (number needed to treat) of four for quetiapine and five for risperidone. The I-squared statistic was 56.1 percent, indicating some heterogeneity. Both Begg’s and Eggar’s test indicated the possibility of publication bias (p=0.002,p=0.002 respectively).

Table 14. OCD—PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Bystritsky et al., 2004 ²⁰⁷	Age 18-65, OCD	26	Placebo-16.9 mg/day Olanzapine-11.2 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Olanzapine vs Placebo-RR = 13.00 (0.81, 209.42)
Shapira et al. 2004 ²⁰⁸	Age 14-70, 1 year duration primary OCD, CGI >= moderate severity, Y-BOCS >= 19	44	Placebo-5.9 mg/day Olanzapine-6.1 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Olanzapine vs Placebo-RR = 1.00 (0.49, 2.03)
Atmaca et al. 2002 ²⁰⁴	Y-BOCS >= 18, OCD, CGI-I minimal improvement	27	Placebo Quetiapine-91.1 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo- RR = 19.60 (1.26, 304.14)
Carey et al. 2005 ²⁰⁵	Age 18-65, Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, CGI-I minimal improvement, CGI = worse	42	Placebo - 228.57 mg/day Quetiapine - 168.75 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo- RR = 0.84 (0.42, 1.69)
Denys et al. 2004 ²⁰³	Age 18-65, Y-BOCS >= 18, Y-BOCS >=12, if only obsessions or compulsions were present, Refractory to SRI therapy	40	Placebo Quetiapine-150 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 4.00 (0.97, 16.55)
Fineberg et al. 2005 ²⁰⁶	Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, Y-BOCS >=18	21	Placebo Quetiapine - 215 mg/day	16 weeks (12 week outcome pooled)	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 2.73 (0.34, 22.16)
Kordon et al. 2008 ¹⁹⁷	Aged 18-65, diagnosis of OCD, Y-BOCS >= 18, treated with an SRI >= 12 weeks and non-responders (< 25% improvement in Y-BOCS)	40	Placebo 100-600 mg/day Quetiapine 100-600 mg/day	12 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 2.11 (0.61, 7.24)
Erzegovesi et al. 2005 ²⁰⁹	Age 18-65, 1 year duration primary condition, Drug-free within 3 weeks, Drug-free for at least 3 wks prior to study entry	45	Placebo Risperidone-0.5 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 2.50 (0.63, 10.00)
Hollander et al. 2003 ²¹⁰	CGI >= 3, SRI therapy >= 12 weeks, >=2 SRI trials of adequate dose and duration	16	Placebo 2.75 mg/day Risperidone 2.25 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 5.73 (0.36, 90.83)
McDougle et al. 2000 ²¹¹	1 year duration primary OCD, CGI >= moderate severity, Refractory to SRI therapy	36	Placebo Risperidone-2.2 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 3.92 (1.26, 12.13)

CGI-I = Clinical Global Impression Scale-Improvement Subscale; OCD = obsessive-compulsive disorder; RR = relative risk; SRI = serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

Figure 19. OCD—responders improving 25–35% on Y-BOCS



Active Controlled Trials. One trial compared an atypical antipsychotic plus SSRI plus CBT to SSRI alone plus CBT for the treatment of OCD.¹⁹⁸ Those receiving the atypical were treatment resistant and therefore sicker than the other group, but did have a mean reduction in Y-BOCS of 10 points. Another trial evaluated quetiapine plus an SSRI compared with clomipramine plus an SSRI.²⁰⁰ Quetiapine augmentation produced a significant reduction in the Y-BOCS score, while clomipramine augmentation did not.

Head-to-Head Trials. One trial evaluated the treatment of OCD with olanzapine versus risperidone;¹⁹⁵ it found no statistically significant differences between treatment groups. Another trial evaluated the treatment of OCD with quetiapine versus ziprasidone both adjunctive with an SRI.²¹² This trial reported a 80 percent improvement in Y-BOCS score for the quetiapine group and a 44.4 percent improvement for the ziprasidone group.

Personality Disorder. Our 2006 CER found promising results for this off-label use. Three PCTs of olanzapine and one of aripiprazole reported efficacy compared with placebo. Since 2006,

several additional trials have been published showing mixed results. These studies are displayed in Table 15.

In 2010, a meta-analysis on the efficacy of antipsychotics in treatment of personality disorders²¹³ was published. It included three studies of olanzapine²¹⁴⁻²¹⁶ and one each of risperidone²¹⁷ and aripiprazole.²¹⁸ It also included several studies of conventional antipsychotics, and pooled all the antipsychotics together, without separating out the effects of atypicals. Therefore, we will not report the results of this analysis.

Borderline Personality Disorder (BPD). Since our initial CER, eight placebo-controlled trials of personality disorders have been published; seven were on BPD. Four of these studies showed an improvement with treatment. Two of these studies involved the same population of patients, first reporting after 8 weeks of treatment and then again after 18 months. In those studies, aripiprazole was the treatment used.^{218,219}

Another study showed improvement when 5–10mg olanzapine was used each day but no change from placebo when 2.5mg was used.²²⁰ A study reporting only the psychotic symptoms associated with BPD found an improvement with quetiapine.²²¹

Of note, the three studies that did not show an improvement used ziprasidone or olanzapine and, though there was no difference in response from placebo, both groups of patients in each study showed improvement overall with the treated patients showing a faster time to response.²²²⁻²²⁴ Studies were too heterogeneous to perform meta-analyses.

Active Controlled Trials. One small RCT of olanzapine versus haloperidol for borderline personality disorders in female inpatients,²²⁵ reported patients in both groups improved considerably regarding hostility, depressive mood, and anxiety. However, differences between groups were not statistically significant.

Observational Study. Our search found only one small pilot study of paliperidone for off-label conditions.²²⁶ Although it is a very small observational study, we include here due to lack of any other relevant data on this drug.

There were eight patients with borderline personality disorder and no other current interfering psychiatric disorder such as psychotic disorders, bipolar disorder, cognitive disorder, major depression or substance abuse. The patients were given paliperidone ER for 12 weeks in a dose of 3–6mg per day. Of the six patients who completed the study, the publication lists that paliperidone was efficacious in reducing global symptoms and “a few core symptoms” of borderline personality disorder. However, there is no specific data regarding these results. There were reports of adverse effects including extrapyramidal symptoms (EPS), insomnia, and agitation, and two patients dropped out of the study, one for noncompliance and the other for gastrointestinal adverse effects.

Schizotypal Personality Disorder. One study measured cognitive symptoms in schizotypal personality disorder and found no significant difference from placebo in those treated with risperidone.²²⁷

Table 15. PCTs for personality disorder

Study/Type	Disorder/ Treatment	N	Dosage/Duration	Measures	Effects/AEs
Nickel, 2006 ^{218/} RCT	Borderline PD/ aripiprazole	52	15mg/ 8 weeks	SCL-90-R, HAM-D, HAM-A, STAXI	Significant changes on most scales of SCL-90-R, HAM-D, HAM-A and all scales of STAXI/
Nickel, 2007 ^{219/} Follow-up observation of RCT above	Borderline PD/ aripiprazole	52	15mg / 18 months	SCL-90-R, HAM-D, HAM-A, STAXI	Greater changes on all SCL-90-R scores, less self-injury
Pascual, 2008 ^{222/} RCT	Borderline PD/ ziprasidone	60	40-200mg (mean 84.1mg)/ 12 weeks	CGI-BPD, HAM-D-17, HAM-A, BPRS, SCL-90-R, Barratt Impulsiveness scale, Buss-Durkee Inventory	No significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms
Schulz, 2008 ^{223/} RCT	Borderline PD/ olanzapine	314	2.5-10mg (mean 7.09mg)/ 12 weeks	ZAN-BPD, SCL-90-R, GAF, SDS, OAS-M, MADRS	No significant difference from placebo
Linehan, 2008 ^{224/} RCT	Borderline PD/ olanzapine	24	2.5-15mg (mean 4.46mg) + DBT therapy/ 6 months	OAS-M, TMR, HAM-D, Somatic Symptom Scale	No significant difference from placebo
Zanarini, 2007 ^{220/} RCT of dose response.	Borderline PD/ olanzapine	451 (150 @2.5m148@ 5-10mg)	2.5-10mg/ 12 weeks	ZAN-BPD	Greater change in ZAN-BPD with 5-10mg of olanzapine
VanDenBroek, 2008 ^{221/} RCT	Borderline PD (psychotic symptoms)/ quetiapine	24	200-600mg/ 8 weeks	BPRS, PANSS, DIS-Q	Superior to placebo on BPRS, PANSS
McClure, 2009 ^{227/} RCT	Schizotypal PD (cognitive symptoms)/ risperidone	31	0.25-2mg/ 10 weeks	Cognitive assessment battery	No significant difference from placebo

BPRS = Brief Psychiatric Rating Scale; CGI-BPD = Clinical Global Impression Scale-Borderline Personality Disorder; DIS-Q = Dissociation Questionnaires; GAF = Global Assessment of Functioning Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; OAS-M = Overt Aggression Scale-Modified; PANSS = Positive and Negative Symptom Scale; PD = personality disorder; RCT = randomized controlled trial; SCL-90-R = Symptom Checklist 90-revised; SDS = Sheehan Disability Scale; STAXI = State-Trait Anger Expression Inventory; TMR = therapist monitoring record; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder

Post Traumatic Stress Disorder(PTSD). Our 2006 CER found six PCTs of atypicals for PTSD. Due to heterogeneity, we could not conduct meta-analysis. Trials for combat-related PTSD reported benefits, while trials in abused woman reported mixed results.

Two systematic reviews on use of atypical antipsychotics as monotherapy or medication augmentation for patients with PTSD^{228,229} were published after our original evidence report. One included five studies of risperidone²³⁰⁻²³⁴ and two studies of olanzapine.^{235,236} It found that atypicals have benefit (compared with placebo) as measured by the change in CAPS score. The publication did not report separate results by drug or clinical subtype. Another review²²⁹ included

10 double-blind RCTs and eight open-label trials. Small positive effects were found for risperidone and quetiapine. Results for olanzapine were mixed.

Our literature search identified three new placebo-controlled trials that assessed risperidone for the treatment of PTSD^{233,237,238} and two of quetiapine.^{239,240} Combined with the studies included in the original CER, there were eight studies of risperidone^{230-234,237,238,241} two studies of olanzapine^{235,236} and two for quetiapine^{239,240} for PTSD. Trials were small, ranging from 15 to 94 participants. Quality scores ranged from two to four on the Jadad scale.

Two trials identified in the new literature search reported on the same trials we included in our previous report.^{233,238} We selected the most current article to include in our new CER.^{233,234} This left 10 trials varying in duration from 5 to 16 weeks. All but two of these trials measured the CAPS. One that did not utilize the CAPS studied showed no difference in improvement between the olanzapine and placebo group.²³⁶ The other found risperidone superior to placebo in reducing irritability and intrusive thought symptoms of PTSD.²³² One risperidone PCT²³³ reported that the treated population showed a significant difference in the CAPS score at endpoint, compared with placebo, but did not report the exact numbers. Similarly, one study reported a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared with placebo.²³⁹ This study did not report exact scores, so could not be pooled in our meta-analysis. Another study found quetiapine/setraline combination superior to setraline plus placebo according to decrease in CAPS score from baseline to 8 weeks.²⁴⁰

Thus, the five remaining PCTs, which were clinically comparable, were pooled in our meta-analyses.^{230,231,234,235,237} The trials are displayed on Table 16. The sample sizes ranged from 19 to 65, while the duration ranged from 5 to 16 weeks, with three trials reporting results at eight weeks. Risperidone dose ranged from 0.5mg to 3mg daily. The one trial of olanzapine used 15mg daily dose.

The similar outcome across these five trials was the CAPS total score. A lower CAPS score indicates fewer PTSD symptoms. Thus, we calculated a weighted mean difference for each study and a positive weighted mean difference means an improvement in CAPS total score from baseline to follow up.

We stratified our analyses first by drug (Figure 20). Only risperidone had enough eligible studies to calculate a pooled estimate.^{230,231,234,237} The random effects pooled estimate for risperidone was 6.47 (95% CI 0.32, 12.61). The one olanzapine study²³⁵ had an effect size of 12.13 (95% CI 0.97, 23.29). The overall random effects pooled estimate for risperidone and the one olanzapine study was 7.79 (95% CI 2.40, 13.17), with an I-squared = 0.0 percent. The clinical importance of this 6- or 12-point weighted mean difference needs to be considered in the context that the range of this instrument is 0–136 points, and the standardized mean differences are 0.40, which is normally considered “moderate” in size.

We also performed a meta-analysis stratified on combat status (Figure 21). We included three studies that included patients with PTSD from combat situations,^{230,234,235} and two studies that primarily included abused women with PTSD.^{231,237} We only had a sufficient number of studies to perform pooled analysis on the combat studies. We found a random effects pooled estimate of 7.95 (95% CI 1.06, 14.84).

Finally, we performed a meta-analysis of the risperidone studies stratified by followup time (Figure 22) divided the studies in to durations greater than or equal to 12 weeks or less than 12 weeks. One study reported outcomes in both time frames,²³⁷ one additional study reported outcomes at 12 weeks or more²³⁰ and two additional studies reported outcomes at less than 12 weeks.^{231,234} We only had a sufficient number of studies to report a pooled effect for the less than

12 week outcomes. The random effects pooled estimate for these three studies was not statistically significant (3.23, 95% CI -5.47, 11.93), indicating that we did not find an improvement in CAPS scores for risperidone treatment over placebo at less than 12 weeks.

Active Controlled Trials. We found no active controlled trials of atypicals for PTSD.

Head-to-Head Trials. We found no head-to-head trials of atypicals for PTSD.

Table 16. PTSD—PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Stein et al. 2002 ²³⁵	PTSD diagnosis, Refractory to SRI therapy	19	Placebo 20.00 mg/day Olanzapine 15.00 mg/day	8 weeks	Difference in CAPS score: Olanzapine vs. Placebo –WMD = 12.13 (0.97, 23.29)
Bartzokis et al. 2005 ²³⁰	Proof of military service, CAPS ≥ 65	65	Placebo Risperidone 3 mg/day	16 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = 9.70 (1.01, 18.39)
Hamner et al. 2003 ²³⁴	Age ≥ 18, Psychosis/psychotic features, PANSS ≥ 60, PANSS with score ≥ 4 on at least 1 item on positive symptoms subscale	40	Placebo Risperidone-2.5 mg/day	5 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = -1.10 (-14.37, 12.17)
Reich et al. 2004 ²³¹	CAPS-1 ≥ 50, PTSD related to childhood physical, sexual, emotional or verbal abuse,	21	Placebo Risperidone-1.41 mg/day	8 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = 11.00 (-8.55, 30.55)
Rothbaum et al. 2008 ²³⁷	18-65, PTSD due to civilian trauma, CAPS ≥ 50	25	Placebo Risperidone 0.5-3 mg/day	8 weeks	Difference in CAPS: Risperidone vs. Placebo – WMD = 4.08 (-10.17, 18.34)

CAPS = Clinician-Administered PTSD Scale; PANSS = Positive and Negative Symptom Scale; PTSD = post-traumatic stress disorder; SRI = serotonin reuptake inhibitor; WMD = weighted mean difference

Figure 21. PTSD—by combat status—difference in CAPS score

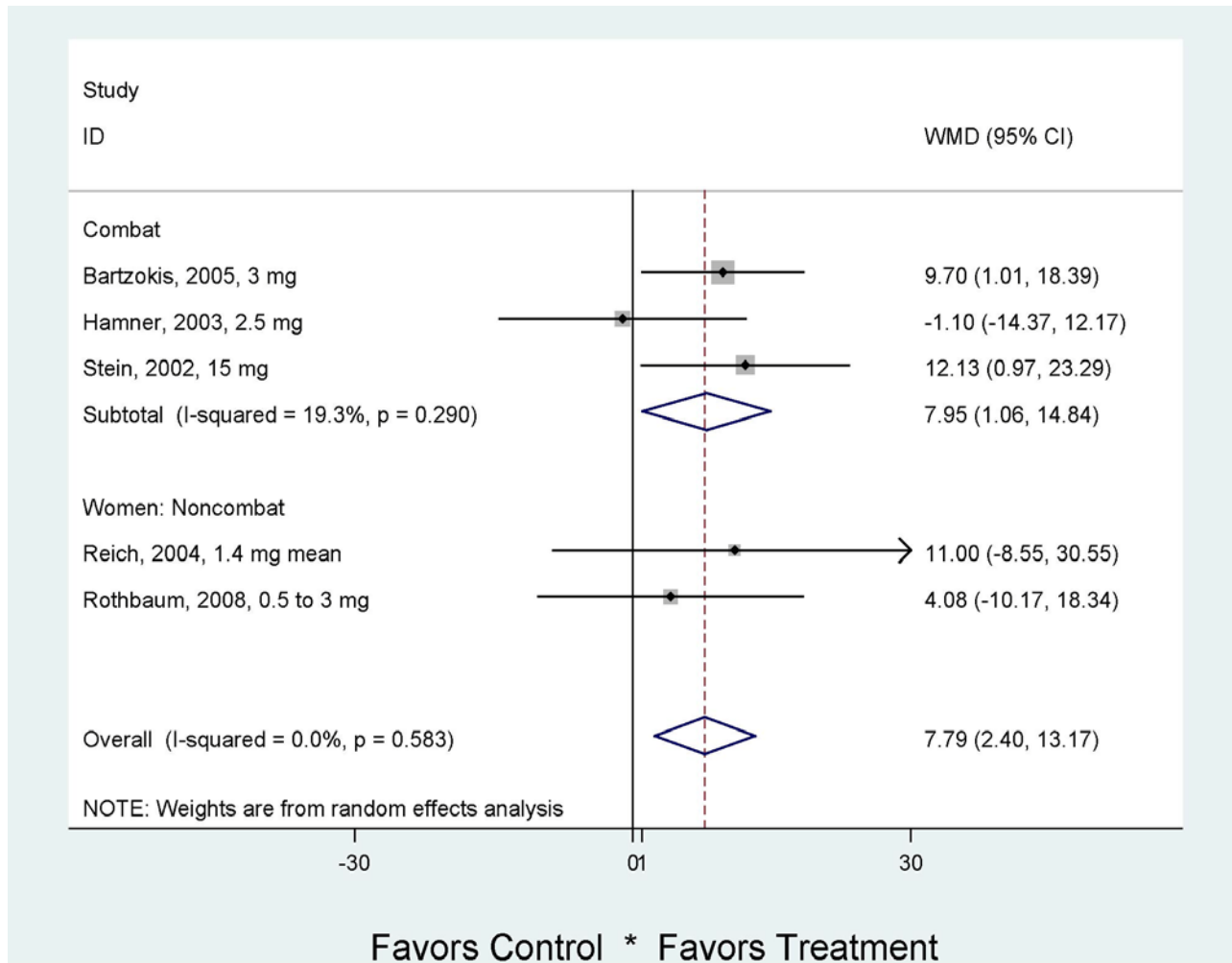
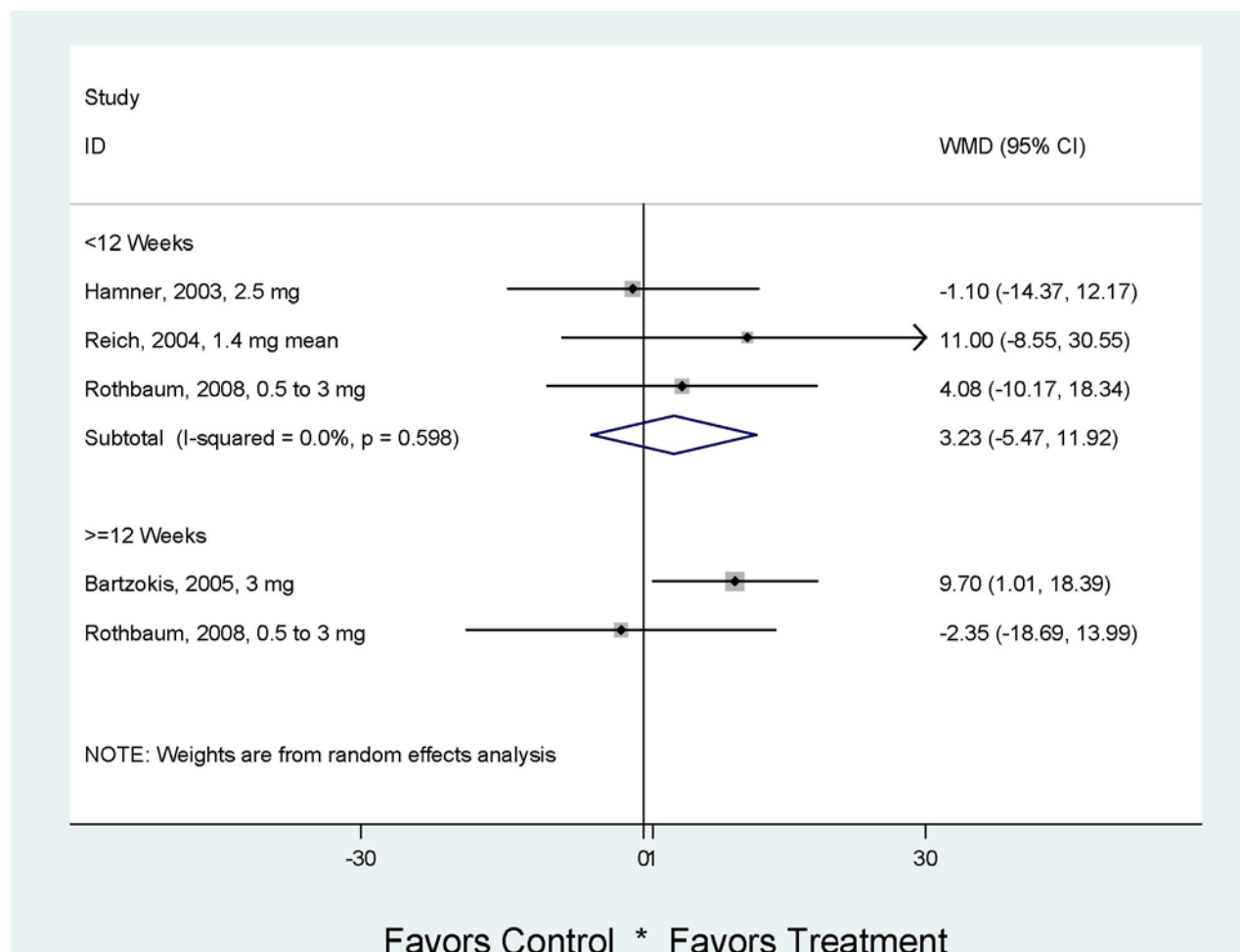


Figure 22. PTSD—by time—difference in CAPS score



Substance Abuse. This off-label use was not included in our 2006 CER. Our literature search identified 33 studies that evaluated the use of atypical antipsychotics for use in alcohol or drug abuse. Nine trials were excluded from further analysis because they included patients with schizophrenia or schizophrenia-related psychosis²⁴²⁻²⁴⁹ or bipolar disorder.²⁵⁰

Of the remaining 24 trials, ten evaluated aripiprazole,²⁵¹⁻²⁵⁴ olanzapine,²⁵⁵⁻²⁵⁸ and quetiapine^{259,260} treatment for alcohol abuse and dependence. Ten trials assessed aripiprazole,^{261,262} olanzapine,²⁶³⁻²⁶⁵ and risperidone²⁶⁶⁻²⁷⁰ treatment for cocaine abuse and dependence. The quality and size of trials varied widely; Jadad scores ranged from 0 to 5, and sample size ranged from 3 to 262 participants.

Two trials assessed aripiprazole versus placebo for amphetamine/methamphetamine abuse^{271,272} and one trial evaluated olanzapine versus an SSRI and benzodiazepine for the treatment of heroin abuse and dependence.²⁷³ The two amphetamine/methamphetamine treatment trials found aripiprazole not likely to be an efficacious treatment.^{271,272} The heroin treatment trial found olanzapine did not improve addictive behavior or relapse.²⁷³ Another trial assessed treatment of concurrent cocaine and heroin dependence with the combination of methadone with risperidone at 2 or 4mg or placebo. This trial found no difference in reduction of cocaine or opiate use, between the three groups.²⁷⁴

Alcohol. The 10 trials that evaluated treatment of alcohol abuse ranged in duration from a few hours to 16 weeks. Two trials reporting on outcomes only after a specified number of drinks or several hours were not included.^{255,258}

The most commonly reported outcome was drinking abstinence, which was reported in seven of the remaining eight trials. The one trial²⁵⁷ that did not report on abstinence compared olanzapine and placebo's effects on alcohol craving. After 2 weeks of treatment, they found that those participants with the longer repeat allele of the DRD4 VNTR gene responded to olanzapine with reduced craving and alcohol use whereas the participants with the shorter alleles did not.

Of the seven trials that reported on abstinence, two did not report sufficient data to calculate an effect size to use in further analyses.^{254,260} In one study,²⁵⁴ aripiprazole was found no better than placebo on the main outcome of percentage of days abstinent. In another study²⁶⁰ there were statistically significant differences for any primary drinking outcomes between patients treated with quetiapine plus naltrexone versus placebo plus naltrexone. Of the remaining trials, two reported only the number or percentage of patients that were completely abstinent at 12 weeks,^{252,259} one reported the number of patients that were completely abstinent and the number or percentage of days abstinent,²⁵² and one trial reported the number of days abstinent.²⁵⁶

We performed meta-analysis for percentage of patients completely abstinent. Results are displayed in Figure 23. Three trials reported the number or percentage of patients completely abstinent during the followup period, which ranged from 8 days to 16 weeks. Two evaluated aripiprazole^{252,253} and one assessed quetiapine.²⁵⁹ The trials are displayed in Table 17. The size of these trials ranged from 30 to 288 participants. The overall random effects pooled estimate of the relative risk of remaining completely abstinent was 1.42 (95% CI 0.36, 5.67). The overall I-squared statistic was 80.4 percent. Neither Begg's nor Eggar's test indicated publication bias ($p = .296$, $p = .308$, respectively).

Active Controlled Trials. One study compared naltrexone with aripiprazole; there was no difference in either mean number of days abstinent or percentage of group completely abstinent.²⁵¹

Cocaine. One published meta-analysis²⁷⁵ assessed use of atypicals in treatment of cocaine dependence. It included three trials of risperidone^{268,270,274} and three of olanzapine.^{245,264,265} Outcome was rate of dropout from residential and outpatient substance abuse treatment programs. The analysis found no significant difference between atypicals and placebo; effect was not reported separately by medication.

Ten trials with placebo comparisons reported on the treatment of cocaine abuse or dependence with aripiprazole,^{261,262} olanzapine,²⁶³⁻²⁶⁵ and risperidone.²⁶⁶⁻²⁷⁰ These trials ranged from several days to 20 weeks. Outcomes reported varied greatly; most consistently reported outcomes were the Cocaine Craving Questionnaire (CCQ) and the ASI-drug. Two trials reported neither the CCQ or the ASI,^{267,268} they were not considered for further analysis. The first reported that risperidone improved neuropsychological impairment in cocaine-withdrawn patients.²⁶⁷ One was an active-control trial that will be discussed below.

Five of the remaining eight cocaine abuse PCTs reported the CCQ.^{261-263,265,270} None reported usable CCQ data that would allow us to calculate an effect size estimate; thus, we could not use the CCQ as a poolable outcome. Five of the eight trials reported the ASI-drug composite score, two of which had no usable data.^{263,266} The first of these compared olanzapine to placebo for 16

weeks. They found that olanzapine was not superior to placebo in decreasing use, cravings, or addiction severity.²⁶³ The second of these compared risperidone to placebo in the treatment of cocaine dependence. There was no reduction in cocaine use after 12 weeks of treatment.²⁶⁶ The remaining three trials were considered comparable enough to justify meta-analysis, pooling on the continuous ASI-drug composite score outcome.^{264,265,269} The trials are listed in Table 18; meta-analyses results are displayed in Figure 24.

These trials of olanzapine^{264,265} and risperidone²⁶⁹ treatment for cocaine abuse ranged in size from 30 to 68 participants and lasted from 8 to 12 weeks. We calculated a weighted mean difference for the effect size estimate in which a positive weighted mean difference favors the treatment arm. The overall random effects pooled estimate for the difference in ASI-drug composite score was 0.001 (95% CI -0.41, 0.043). The I-squared statistic indicated no heterogeneity. Neither Begg's nor Eggar's test indicated publication bias (p=1.00,p=0.928 respectively).

Active Controlled Trials. We found one trial that compared risperidone with pergolide.²⁶⁸ There was no statistical difference from placebo in reducing cocaine use.

Table 17. Alcohol abuse—PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Anton et al. 2008 ²⁵²	21-65 years old, alcohol dependence, present at 3 visits with negative breathalyzer results and abstain from alcohol before randomization Score < 8 on Clinical Institute Withdrawal Assessment for Alcohol Revised	295	Placebo 27.4 mg/day Aripiprazole 2-30 mg/day	12 weeks	Alcohol complete abstinence: Aripiprazole vs Placebo – RR = 0.50 (0.29 , 0.88) Abstinent days: Aripiprazole vs Placebo – SMD=-0.13(-0.36, 0.10)
Voronin et al. 2008 ²⁵³	Aged 21-65, alcohol dependence, non treatment seeking	30	Placebo Aripiprazole 5-15 mg/day	8 days	Alcohol complete abstinence: Aripiprazole vs Placebo - RR= 1.67 (0.48 , 5.76)
Kampman et al. 2007 ²⁵⁹	Aged >= 18 years old, alcohol dependence, have a consecutive 30 days period drinking at least 48 standard drinks, >= 2 days of heavy drinking, >= 3 consecutive days of abstinence, Clinical Institutes Withdrawal Assessment for Alcohol score < 8	61	Placebo 50-400 mg/day Quetiapine 50-400 mg/day	12 weeks	Alcohol complete abstinence: Quetiapine vs Placebo - RR = 4.97 (1.17 , 21.11)

RR = relative risk; SMD = standardized mean difference

Figure 23. Substance abuse—alcohol complete abstinence

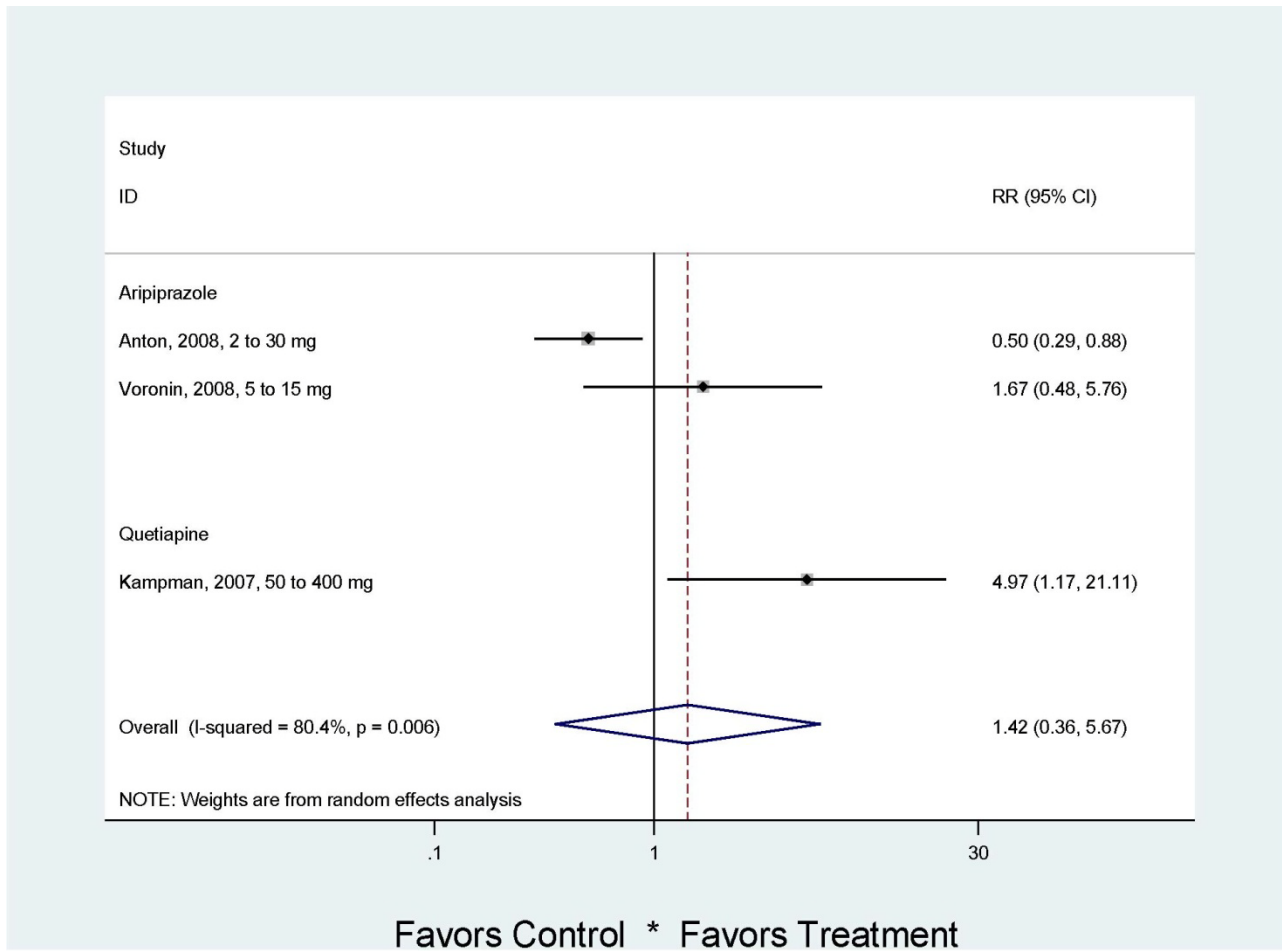
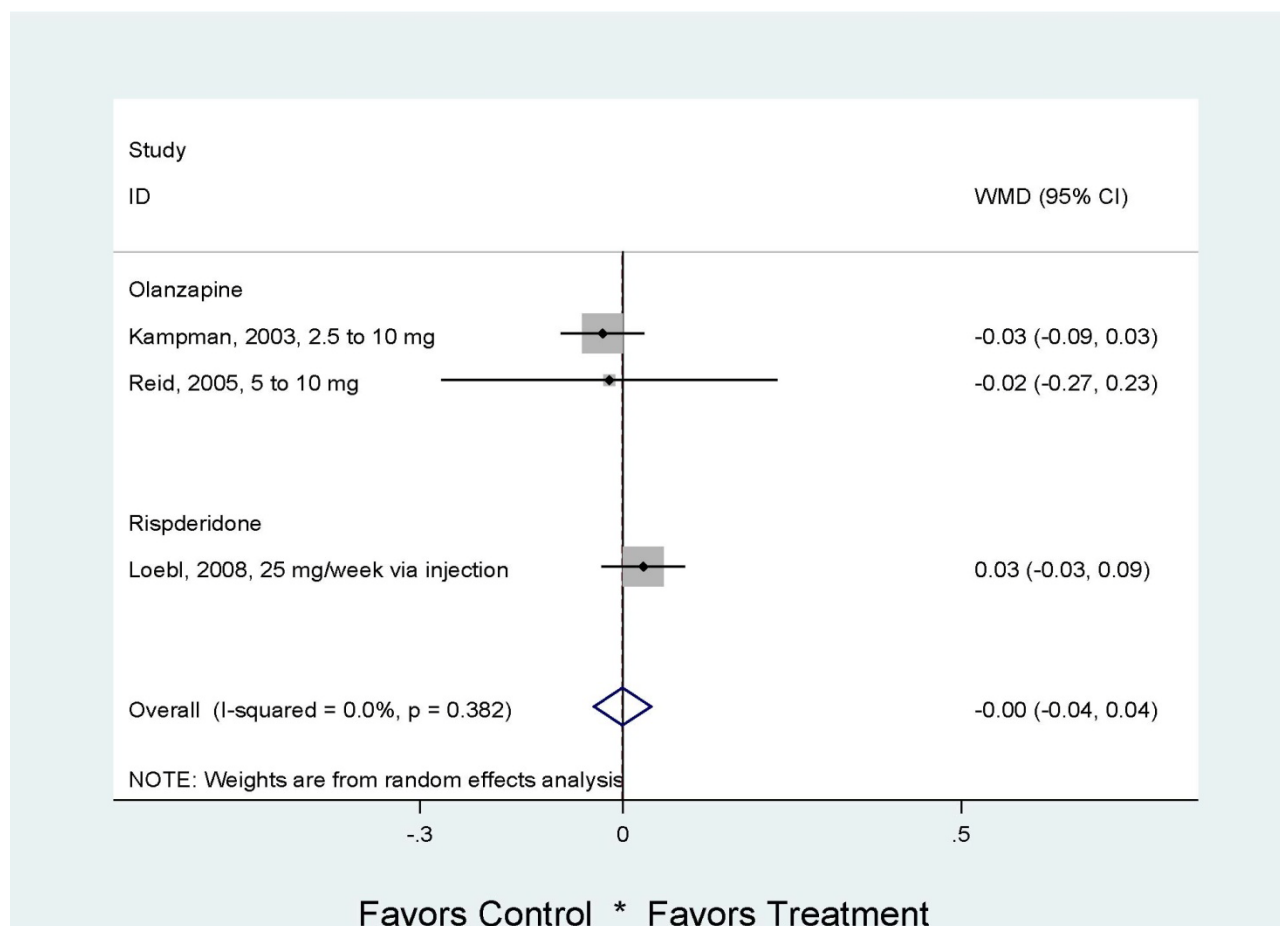


Table 18. Cocaine—PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Kampman et al. 2003 ²⁶⁴	\$100 worth of cocaine use in prior month, age 18-60, cocaine dependency	30	Placebo 2.5-10 mg/day Olanzapine 2.5-10 mg/day	11 weeks	Change in ASI: Olanzapine vs Placebo – WMD = 0.03 (-0.03 , 0.09)
Reid et al. 2005 ²⁶⁵	Standardized CREST study inclusion criteria	68	Placebo 2 tablets/day Olanzapine 5-10 mg/day Valproate 800-1500 mg/day Carnitine + CoQ 10 200+500 mg/day	8 weeks	Change in ASI: Olanzapine vs Placebo - WMD = 0.02 (-0.23 , 0.27)
Loebl et al. 2008 ²⁶⁹	Men, 18-60, cocaine dependence, using cocaine >=1 every other week	31	Placebo Risperidone 1-2 mg daily / 0-3 weeks utilized only during initiation of risperidone longacting injection Risperidone long-acting injection 25mg every two weeks	12 weeks	Change in ASI: Risperidone vs Placebo - WMD = -0.03 (-0.09 , 0.03)

ASI = Addiction Severity Index; CREST = Cocaine Rapid Efficacy Screening Trial; WMD = weighted mean difference

Figure 24. Cocaine—ASI drug composite



Tourette’s. We found no new clinical trials that studied atypical antipsychotics for Tourette’s syndrome published after our original CER. That CER reported risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared with placebo.

There were two observational studies^{276,277} of aripiprazole that reported effectiveness data after our 2006 CER; information is displayed in Table 19. One was a retrospective observational study for the treatment of tics with or without comorbid explosive disorder. Thirty-seven patients aged 8–18 years old were treated with aripiprazole 2.5-40 mg for 12 weeks. All of the 29 subjects who completed the trial experienced a reduction in their tic severity. However, eight subjects discontinued early due to inability to tolerate the medication.²⁷⁶

The other study treated 24 patients, aged 7–18 years old with a mean aripiprazole dose of 9.8mg for eight weeks. Overall, there was a 52.8 percent reduction in Yale Global Tic Severity Scale scores, and 19 of the 24 were described as “much” or “very much” improved per CGI-I. Six of the patients discontinued due to adverse effects.²⁷⁷

Table 19. Atypical antipsychotics for Tourette’s syndrome

Study/Type	Patients/Age	Dosage/Duration	Measures	Effects
Budman, 2008 ²⁷⁶ / Retrospective observational study	37 patients (29 completed, 8 withdrew for inability to tolerate)/ 8-18 years	2.5-40mg (mean 11.69)/ 12 weeks	CGI- Tics	Reduction in tic severity in 100% of subjects
Yoo, 2007 ²⁷⁷ / Open-label, flexible dosing	24 patients (18 completed, 6 withdrew for adverse effects)/ 7-18 years	9.8 mg (+/- 4.8)/ 8 weeks	YGTSS, CGI-I, CGI- S, adverse effects checklist, EPS rating scale, height and weight, labs, ecg	52.8% reduction in mean YGTSS scores overall CGI-I much improved or very much improved in 19/24

CGI-I = Clinical Global Impression Scale-Improvement Subscale; CGI-S = Clinical Global Impression Scale-Severity Subscale; EPS = extrapyramidal symptoms; YGTSS = Yale Global Tic Severity Scale

Discussion

We conducted an extensive literature search, data abstraction, and meta-analyses whenever possible to assess the efficacy and comparative effectiveness of atypical antipsychotics for off-label use. Since the publication of our original CER in 2006, many new high-quality controlled trials have been published; we were able to add many to our prior quantitative analyses. Our results are summarized in Table 20. It is important to note that we found no trials of the three newest atypicals—asenapine, iloperidone, and paliperidone—for off-label uses.

We found that aripiprazole, olanzapine, and risperidone had small but statistically significant effects in treating agitation, psychosis, and behavioral symptoms of dementia. Because of the plethora of trials, the large sample sizes enrolled in each trial (usually 300 or more), the quality of trials (mean Jadad score 3.2) and the consistency of the results, the strength of the evidence is high. However, the clinical benefits must be balanced against significant side effects and potential harms. (See results of Key Question 4, later in this report.) In addition, most trials used flexible dosing, so we were unable to determine the most appropriate dosage.

Moderate strength evidence suggests efficacy of aripiprazole, quetiapine, and risperidone as augmentation in treatment of MDD in patients who respond inadequately to SSRIs/SNRIs. Effect sizes are moderate to large, with patients one and a half to two times as likely to respond as with SSRIs alone. Also, a few trials found efficacy for ziprasidone and olanzapine; the strength of evidence is low for these two drugs, but this rating could change with the publication of additional successful trials. Quetiapine is also effective as monotherapy for MDD; strength of evidence is moderate. Strength could increase to high if non–industry-funded studies are published with similar results.

We found moderate strength evidence of efficacy of risperidone as augmentation therapy for OCD. Trials for OCD tend to be much smaller than those for dementia and depression; sample sizes ranged from 15 to 45 for the 10 trials contributing to our efficacy meta-analysis. The mean quality of trials is lower (2.2 on Jadad scale). Results are also less consistent. For example, in the only two PCTs of olanzapine, percentage of participants responding as measured by Y-BOCS did not differ from placebo. In contrast, a head-to-head trial (with no placebo) found no difference in efficacy between olanzapine and risperidone, a drug with moderate evidence of efficacy.

There is also moderate strength evidence of efficacy in reducing symptoms of combat-related PTSD from several small trials of risperidone. We also found two studies of olanzapine for PTSD; they reported conflicting results. There is low strength of evidence based on two positive

trials of quetiapine. Trials of PTSD tend to be of lower quality and smaller size than the depression augmentation and dementia trials. Mean Jadad score was 2.7; only two PTSD trials had over 40 participants. New, preferably larger trials must be conducted before the strength of evidence can be increased.

Regarding borderline personality disorder, strength of evidence of efficacy is low or very low for all atypicals other than risperidone, where we found no trials. Olanzapine had the most trials (seven) but results were inconsistent. Of note, however, in the olanzapine studies that showed no difference between drug and placebo groups at 12-week followup, both groups of patients showed improvement overall, with the treated patients showing a faster time to response.

We added eating disorders, anxiety, insomnia, and substance abuse to our 2011 report. With the exception of generalized anxiety disorder, there is little scientific evidence that atypicals are useful in addressing symptoms of these conditions. Moderate evidence suggests that olanzapine, risperidone, and aripiprazole have no efficacy in substance abuse treatment, and that olanzapine treatment does not lead to weight increase in eating disorder patients, compared with placebo. We did find moderate evidence of efficacy of quetiapine in treating generalized anxiety disorder. There were too few trials of olanzapine, risperidone or ziprasidone for anxiety to pool; these trials had mixed results. Importantly, anxiety trials had larger samples (mean N = 122) and higher quality (mean Jadad score = 3.1) than most trials for OCD, PTSD, substance abuse, and eating disorders.

Finally, we reviewed trials of children and adolescents with Tourette's syndrome or ADHD; evidence of efficacy was low for use of atypicals for these conditions. No Tourette's trials have been published since our 2006 CER which reported that risperidone is at least as effective as pimozide or clonidine. Only one small trial has studied atypicals for ADHD in children with no major co-occurring disorders; risperidone users were more likely to respond than placebo patients.

These findings are valuable and can help psychiatrists make better clinical decisions based on the latest evidence. Findings are summarized in Table 20. The symbol "O" below indicates areas where we found no clinical trials of a particular atypical for that condition, while "--" indicates evidence of inefficacy for a condition, according to the psychometric measures our team considered most important. In summary, ziprasidone has no evidence of efficacy for any off-label use other than depression. The four other atypicals have shown efficacy in treating dementia, depression, and a few other conditions, depending on drug.

Table 20. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety					
- generalized anxiety disorder	O	-	++	-	-
Anxiety					
- social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder					
-no co-occurring disorders	O	O	O	+	O
Attention Deficit/Hyperactivity Disorder					
-bipolar children	-	O	O	O	O
Attention Deficit/Hyperactivity Disorder					
-mentally retarded children	O	O	O	+	O
Dementia overall	++	+	+	++	O
Dementia psychosis	+	+-	+-	++	O
Dementia agitation	+	++	+-	++	O
Depression					
-MDD augmentation of SSRI / SNRI	++	+	++	++	+
Depression					
-MDD: Monotherapy	O	-	++	O	O
Eating Disorders	O	--	-	O	O
Insomnia	O	O	-	O	O
Obsessive Compulsive Disorder					
-augmentation of SSRI	O	+	--	++	-
Obsessive Compulsive Disorder					
-augmentation of citalopram	O	O	+	+	O
Personality Disorder					
-borderline	+	+-	+	O	-
Personality Disorder					
-schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder	O	+-	+	++	O
Substance Abuse alcohol	--	-	-	O	O
Substance Abuse cocaine	O	-	O	-	O
Substance Abuse methamphetamine	-	O	O	O	O
Substance Abuse methadone clients	O	O	O	-	O
Tourette's Syndrome	O	O	O	+	-

++: moderate or high evidence of efficacy

+: low or very low evidence of efficacy

+-: mixed results

-: low or very low evidence of inefficacy

--: moderate or high evidence of inefficacy

O: no trials

: Approved by FDA for the indication

MDD = major depressive disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Note: Symbols denote strength of evidence, not size of potential effect. For example in dementia “++” indicates moderate-to-high strength of evidence that there is a beneficial effect, however the size of the effect is small.

Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, the possibility of publication bias still exists. Table 21 below displays our assessment of heterogeneity by condition and outcome. For the most part, our assessment did not yield evidence of unexplained heterogeneity. Two exceptions include the MADRS for depression and the Y-BOCS (percent of participants responded) outcome used in our OCD meta-analysis. In our analysis of atypicals as augmentation and monotherapy in treatment of major depressive disorder (MDD), possible publication bias appeared in studies reporting the MADRS (Begg's $p=.072$, Egger's $p=.019$ for augmentation, percent remitted; Begg's $p=.027$, Egger's $p=.027$, for monotherapy, percent responded). We conducted additional augmentation meta-analyses using HAM-D outcomes; efficacy results were similar, but no heterogeneity was detected. Thus, our confidence that some atypicals have efficacy in treating depression remains. Heterogeneity was also evident in studies assessing the efficacy of atypicals for OCD (Begg's $p=0.002$, Egger's $p=0.001$). This heterogeneity was likely due to patient enrollment criteria; studies used different definitions of "refractory" and "treatment resistant." Another published meta-analysis of atypicals for OCD¹⁹² found similar efficacy results but no heterogeneity according to statistical tests.

Table 21. Analysis of publication bias

Condition	Outcome	Begg's Test P-Value*	Egger's Test P-Value
Anxiety	HAM-A % Responded	0.462	0.239
Dementia	Total/Global Scores	0.837	0.790
Dementia	Psychosis	0.558	0.429
Dementia	Agitation	0.544	0.178
Depression, Augmentation	HAM-D % Remitted	0.771	0.245
Depression, Augmentation	HAM-D % Responded	0.711	0.245
Depression, Augmentation	MADRS % Remitted	0.072	0.019
Depression, Augmentation	MADRS % Responded	0.260	0.069
Depression, Monotherapy	MADRS % Remitted	0.860	0.142
Depression, Monotherapy	MADRS % Responded	0.027	0.027
Eating Disorders	BMI	0.730	0.680
OCD	Y-BOCS % Responded	0.002	0.001
PTSD	CAPS	0.806	0.608
Substance Abuse	Alcohol Complete	0.296	0.308
Substance Abuse	Abstinence		
Substance Abuse	ASI Drug Composite	1.000	0.928

*** Continuity Corrected**

ASI = Addiction Severity Index; BMI = body mass index; CAPS = Clinician-Administered PTSD Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

An important limitation common to systematic reviews is the quality of the original studies included. In order to measure the quality of clinical trials we used the Jadad scale.¹⁷ As empirical evidence regarding other study characteristics and their relationship to bias is lacking, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. In our 2006 CER on off-label use of atypicals, we conducted a sensitivity analysis on the relationship between trial quality and effect size; the better quality trials reported an effect size 25 percent smaller than did lower quality trials. This finding increases the likelihood that a synthesis of results of all studies—whether narrative or quantitative—may produce inflated estimates of efficacy. As

stated above, the higher general quality of the dementia and depression augmentation studies led to a greater strength of evidence rating for those uses.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals must be known to assess applicability. Such data were reported unevenly in the studies we reviewed. The dementia trials were most often conducted in nursing homes, hospitals, or assisted living facilities. According to our review on utilization patterns, these settings represent where atypicals are most often used in the elderly. Studies for other conditions were not particularly representative. For example, three of the four trials for ADHD were conducted in children with severe co-occurring conditions, such as bipolar disorder or mental retardation. Subjects in substance abuse trials were usually enrolled in outpatient or residential treatment programs. However, there was one trial of non-treatment-seeking subjects;²⁵³ it is unlikely that atypicals would be used in the real world without some initial detoxification or simultaneous treatment program.

In the studies of atypicals as augmentation for SSRI or SNRI patients with MDD, it was often unclear whether patients were simultaneously undergoing psychotherapy. One article¹⁶⁵ specifically stated that subjects were prohibited from initiating such therapy during the trial, but other articles were unclear on the issue. Thus, we don't know whether treatment over and above the medication influenced the study results. It is important to note that subjects in depression trials were recruited from both primary care and mental health centers, as depression patients have been increasingly treated in primary care settings.

We found only one small trial (N=13) of atypicals for treatment of insomnia. Observational studies of Insomnia included patients with Parkinson's disease, MDD, polysubstance abuse withdrawal symptoms, and tamoxifen-induced insomnia. Thus, the results of these studies should not be applied to the general population.

Key Question 3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Points

There was no difference in effect by gender in one study of aripiprazole for MDD. No other studies stratified results by gender.

Atypicals may have greater efficacy in male combat veterans than in civilian women with PTSD.

There are insufficient data to make conclusions regarding differences in efficacy by patient age. Two studies of atypicals for MDD in older adults found them at least as efficacious as in studies conducted in the non-elderly.

There are insufficient data to make statements regarding treatment effects by race/ethnicity, as no studies reported stratified results.

Differing measures of disease severity preclude overall conclusions about the effects of atypical antipsychotics by severity.

Detailed Analysis

There was only one study that conducted subgroup analysis by gender. In that trial, aripiprazole was used as an adjunct in treatment of major depressive disorder. Regarding mean

change in MADRS total score, there were no statistically significant interaction effects for gender.¹⁵⁴

Trials of PTSD were conducted in male and female populations. In the male trials^{230,234,235} PTSD was combat-related, while the female trials^{231,237} were conducted on civilian women whose PTSD was abuse-related. In pooled analysis of the three combat studies, mean difference in CAPS was 7.95 (95% CI 1.06, 14.84) compared with placebo. Although we could not pool the results of the two trials in abused women, we note that the results of both trials were not statistically different from placebo.

There were no trials that stratified by race; therefore evidence about the differing benefits by race was not obtained.

Regarding age, as expected, most participants in ADHD and Tourette's trials were children or adolescents, while trials for dementia were conducted in the elderly. As these conditions are heterogeneous and use different measures of efficacy, it is not possible to compare efficacy by age group. There were no trials that specifically stratified effects by age; however, there were two depression trials conducted in an older population. One studied risperidone augmentation in patients ≥ 55 years old.²⁷⁸ The authors found a suggestion towards greater symptom resolution with risperidone (compared with placebo augmentation) but no significant difference in time to relapse. Reported side effects included headache, dizziness and dry mouth. The other trial studied quetiapine monotherapy in patients with depression >65 years old.¹⁶⁹ The relative risk of remitting on the MADRS for those participants taking quetiapine compared with placebo was 2.48 (95% CI 1.70, 3.62); the relative risk of responding on the MADRS for those patients in the quetiapine arm versus the placebo arm was 2.11 (95% CI 1.63, 2.71). These estimates of effect size were larger than all other studies included in our depression meta-analyses (see Key Question 2). Reported side effects included somnolence, headache, dry mouth, dizziness, fatigue, insomnia, constipation, diarrhea, nausea, weight increase, sedation, asthenia, extrapyramidal disorder, upper abdominal pain, back pain and dysgeusia.

There was insufficient data to conduct analyses by disease subtype, other than the PTSD analysis on combat versus civilian trauma noted above.

Studies differed in the psychometrics used to measure severity of illness, making comparisons across studies difficult. This may reflect the differing definition of disease severity seen clinically.

Discussion

In summary, there are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypical antipsychotic medications. Only one study conducted a subgroup analysis by gender; there were no studies that stratified by racial or ethnic group. Although many studies specified age in their inclusion criteria, no studies stratified results by age. Unfortunately, this limits the conclusions that can be determined.

Examination of the literature for differing effects of atypical antipsychotic medications by clinical subsets did not reveal studies reporting subgroup analyses. Our own meta-analysis found efficacy for combat-related PTSD in men but not for PTSD in civilian women. Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any condition.

Overall, there are not enough data to suggest that a particular subset of the clinical populations, whether by demographic or illness characteristics, will show differing benefit in treatment with atypical antipsychotic treatment. More research in this area is needed.

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Points

We found no trials or large observational studies of asenapine, iloperidone, or paliperidone for off-label uses.

Elderly patients—dementia studies. Our 2006 systematic review discussed a published meta-analysis of atypicals and death in Alzheimer’s disease patients which included both published and unpublished trials. Death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics compared with 2.3 percent of patients randomized to receive placebo. The difference in risk for death was small but statistically significant.

We found six large high-quality cohort studies that compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the cohort studies that made that comparison.

We used data from PCTs to conduct a meta-analysis on symptoms we categorized as cardiovascular (including “cardiovascular symptoms,” “edema,” and “vasodilatation”). These events were reported significantly more often in patients taking olanzapine and risperidone than in those taking placebo. Quetiapine and aripiprazole were not statistically associated with these symptoms.

We conducted a specific analysis on cerebrovascular accident (CVA); risperidone was the only drug associated with an increase. However, as mentioned in our 2006 report, an industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients found the incidence of cerebrovascular adverse events three times as high in olanzapine patients as in placebo patients.

Our meta-analysis of PCTs found olanzapine and risperidone statistically associated with increases in appetite/weight. As reported in 2006, in one large head-to-head trial, Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease (CATIE-AD), elderly patients with dementia who were treated with olanzapine, quetiapine, or risperidone averaged a monthly weight gain of 1.0, 0.7 and 0.4 pounds while on treatment, compared with a weight loss among placebo-treated patients of 0.9 pounds per month.

Olanzapine was associated with unspecified anticholinergic events in one trial.

Our meta-analysis of PCTs also found that aripiprazole, olanzapine, quetiapine, and risperidone were each associated with both sedation and fatigue in dementia patients. Risperidone was associated with an increase in EPS; aripiprazole and quetiapine were not. These findings echo those of our prior analyses and the CATIE-AD trial results. In the one PCT of olanzapine that reported EPS, subjects in the drug group were more likely to report these symptoms.

Endocrine adverse events are a new focus. Only one trial in elderly dementia patients reported these outcomes; there was no difference in diabetes onset or prolactin measures between patients taking risperidone and those taking placebo. One cohort study followed elderly patients enrolled in olanzapine trials; the authors found that the risk of diabetes was not significantly associated with antipsychotic treatment, but rather depended on having an elevated glucose at baseline. Olanzapine, quetiapine and risperidone were associated with urinary symptoms.

We found no trials or large observational studies of ziprasidone for dementia in older adults; therefore, we can not make conclusions regarding safety of ziprasidone in this population.

In head-to-head trials of atypicals, olanzapine patients had higher odds of neurological symptoms, such as headaches and dizziness, than those taking risperidone. A recent publication from the CATIE-AD trial reported cognitive decline in elderly dementia patients treated with olanzapine, quetiapine, or risperidone.²⁷⁹ There was a trend toward greater odds of sedation with olanzapine and quetiapine compared with risperidone. In one trial more risperidone patients than quetiapine patients reported musculoskeletal problems.

We found one new trial comparing adverse events in elderly patients taking either risperidone or SSRIs for depression. There was no difference in adverse events. As reported in our 2006 evidence review, one trial of olanzapine versus benzodiazepines in 205 patients also showed no significant difference in adverse events.

Adults (Age 18 to 64)—studies of anxiety, depression, eating disorders, OCD, PTSD, personality disorders and substance abuse. The only significant difference in cardiovascular symptoms between atypicals and placebo involved blood pressure changes in patients taking quetiapine. No studies of any drug or condition reported CVA.

Our analysis of PCTs found that aripiprazole, olanzapine, quetiapine, and risperidone were each associated with increases in appetite/weight gain. Ziprasidone was not significantly associated with weight gain in two trials. We also found a recently published cohort study of depression treatment which reported risperidone, quetiapine, olanzapine, and ziprasidone, but not aripiprazole, were associated with an increase in the risk of incident hyperlipidemia. In our analysis of three quetiapine PCTs which reported abnormalities in triglycerides, they were more common in patients taking the drug than those taking placebo.

Endocrine and diabetes are a new focus. Two PCTs of olanzapine reported endocrine adverse events; patients taking the drug had increased odds. One PCT each of quetiapine, risperidone, and ziprasidone also reported these events. We were unable to conduct meta-analysis; however, the events were always more prevalent in the atypical group. Six PCTs of quetiapine reported diabetes outcomes; in our pooled analysis there was no statistical difference between patients taking quetiapine and those taking placebo. In the one PCT of olanzapine that reported diabetes outcomes, 5 of the 370 intervention patients became diabetic, compared with only one of the 377 patients taking placebo. In one head-to-head trial, olanzapine had a higher risk for precipitating diabetes than did risperidone. As reported in our 2006 evidence review, one large observational study reported lower odds of diabetes in risperidone subjects than in placebo.

Our analyses indicate that all atypical antipsychotics are associated with an increase in at least some symptoms categorized as neurological (“confusion,” “dizziness,” “headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” and “tinnitus”) when compared with placebo. All but risperidone were associated with increased fatigue; all were associated with sedation. Aripiprazole was associated with increased odds of akathisia, while the other drugs were not. Aripiprazole, quetiapine, and ziprasidone were associated with increased odds of EPS.

Quetiapine patients had higher odds of decreased salivation, neurological events, sedation, and agitation, compared with risperidone patients in two head-to-head trials. Another head-to-head trial reported higher odds of weight gain with olanzapine when compared with ziprasidone.

We found two trials of olanzapine versus a mood stabilizer. Olanzapine patients had lower GI adverse effects, low platelets and mania, but higher odds of weight gain, dry mouth, liver function test abnormality, EPS, and sedation. We found one small trial of quetiapine versus a mood stabilizer: quetiapine patients were less likely to experience EPS.

Two trials of quetiapine, one of risperidone and three of olanzapine reported adverse events compared with SSRIs. Although there were no differences in diabetes rates, higher rates of metabolic lab abnormalities were reported in one trial of quetiapine versus SSRI. Fatigue was more common in olanzapine, quetiapine, and ziprasidone than in SSRIs, and sedation was more common in olanzapine and quetiapine patients. Olanzapine and risperidone patients also had higher odds of cardiovascular adverse events.

Four trials of olanzapine and one of aripiprazole compared adverse events in conventional versus atypical antipsychotics. Weight gain was more common among both olanzapine and aripiprazole patients than those taking conventional antipsychotics. In one trial, olanzapine patients were less likely to observe cardiovascular symptoms, fever/infection, gastrointestinal, and musculoskeletal problems fatigue, akathisia, EPS, and sedation. The four olanzapine trials were pooled; patients were less likely to experience EPS than patients on conventional antipsychotics. In the one aripiprazole trial, fewer aripiprazole patients experienced akathisia and EPS than those on conventional antipsychotics.

Two of the findings potentially differ from the perceptions of psychiatrists. In four studies containing 1,387 patients, aripiprazole was associated with increased appetite/weight gain, and in seven studies including 2,566 patients, quetiapine was associated with EPS. We consider these findings to be a signal deserving of further investigation.

Children & adolescents—studies of ADHD and Tourette’s syndrome. There were no trials or large cohort studies of olanzapine or quetiapine for ADHD or Tourette’s syndrome in children/adolescents, nor were there any head-to-head trials of atypicals for these uses.

Maximum trial length was 6 weeks, and adverse events were few. Weight gain was more common in patients taking risperidone than those taking placebo in two PCTs. In one small PCT, EPS was less common in aripiprazole patients than placebo patients.

In one small PCT of ziprasidone, there were no significant differences in adverse events between groups. In one small trial of clonidine versus risperidone there were no significant differences in adverse events between groups. In one trial of haloperidol versus risperidone significantly more patients on the conventional antipsychotic reported sleep problems.

Detailed Analysis

One of the major rationales for preferring treatment with atypical antipsychotics over conventional antipsychotics is potentially greater safety. To assess this, we abstracted adverse event data from all RCTs of atypicals for off-label conditions, plus observational studies with more than 1,000 subjects. We conducted separate analyses for placebo comparisons, active comparisons (comparing atypical antipsychotics to acetyl cholinesterase inhibitors, benzodiazepines, clonidine, conventional antipsychotics, mood-stabilizers, SRIs, and tricyclic antidepressants), head-to-head trials of atypicals, and observational studies. Of the 128 RCTs

published since our 2006 CER, 115 reported adverse events. We pooled the new data with data from the 65 RCTs included in our 2006 adverse events analyses.

As in the 2006 analyses, we identified and grouped adverse events into clinically relevant categories. These categories were then pooled within three condition categories, based on patient age. Patient age was a proxy measure for the baseline likelihood of adverse events; in other words, children, non-elderly adults, and older adults are expected to have different types of risks for adverse events. Thus, we analyzed studies of dementia patients separately (mean age = 81.5 years); pooled ADHD and Tourette's patients together; and pooled studies of the remaining conditions together (mean ages from 24.3 years for eating disorders to 47.4 years for depression). We did not pool different atypicals together; instead, we generated separate estimates for each of the five atypical antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Again, we found no trials of the three newer drugs (asenpine, iloperidone, paliperidone) for off-label uses.

The complete results of the adverse event analyses are presented in Appendix G. Number needed to harm (NNH) is presented where applicable. For many of the comparisons, the numbers of trials are few and the number of enrolled patients is small, resulting in wide 95 percent confidence intervals and the inability to draw conclusions. However, even with this limitation, many observations are worth noting.

Dementia. Data from trials: There were no trials or large observational studies of ziprasidone in dementia; thus, we have no data on ziprasidone's safety in the elderly.

In 2005, the FDA issued a Public Health Advisory for treatment of dementia with atypical antipsychotics after studies reported increased risk of death compared with placebo. Our 2006 CER discusses a published meta-analysis of atypical antipsychotic medication use and death in Alzheimer's disease patients which included both published and unpublished trials. Fifteen RCTs were included (eight were cited only as abstracts): four trials of risperidone, five of olanzapine, three of quetiapine, and two trials of aripiprazole. In all, 3,353 patients received an atypical antipsychotic, and 1,757 received placebo. With one exception, trials lasted from 6-12 weeks. (The one exception was 26 weeks.) Death occurred in 118 or 3.5 percent of patients randomized to receive atypical antipsychotics versus 40 or 2.3 percent of patients randomized to receive placebo. The odds ratio for death using a fixed effects model was 1.54, with a 95 percent confidence interval of 1.06 to 2.23. The difference in risk for death was small but statistically significant ($p = .01$). In other words, the number needed to harm was 100, although the 95 percent confidence intervals were broad. Pooled data from two trials containing a haloperidol treatment arm indicated that treatment with this conventional antipsychotic was also associated with a similar, albeit not statistically significant, increase in death. The authors concluded that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. As this meta-analysis was well-conducted and included more trials that were available to us, we did not conduct our own meta-analysis of mortality and atypical antipsychotic use for dementia.

In this update, we conducted a meta-analysis on the group of symptoms we categorized as cardiovascular (including "cardiovascular symptoms," "edema," and "vasodilatation"). They were reported significantly more often in patients taking olanzapine and risperidone than in those taking placebo (OR of 2.33, and 2.08, respectively). The number needed to harm (see Table 22) was 48 for olanzapine and 34 for risperidone. Aripiprazole and quetiapine were not statistically associated with these symptoms. We conducted a specific analysis on CVA; risperidone was the

only drug associated with an increase. The pooled odds ratio was 3.12 (95% CI 1.32, 8.21); number needed to harm was 53.

Table 22. Cardiovascular adverse events among dementia patients—atypical antipsychotics compared with placebo

Adverse Events	Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
		# of studies	# adverse events	sample size	# adverse events	sample size			
Cardiovascular/CVA	Olanzapine	2	4	232	6	278	1.46	0.33, 7.44	NC
Cardiovascular/CVA	Risperidone	4	8	753	24	1099	3.12	1.32, 8.21	53
Cardiovascular/CVA	Aripiprazole	3	2	253	2	340	0.70	0.05, 10.48	NC
Cardiovascular/CVA	Quetiapine	2	6	241	3	185	0.65	0.10, 3.08	NC
Cardiovascular – other	Olanzapine	5	9	440	40	778	2.33	1.08, 5.61	48
Cardiovascular – other	Risperidone	6	34	1010	119	1757	2.08	1.38, 3.22	34
Cardiovascular – other	Aripiprazole	1	12	121	42	366	1.18	0.58, 2.55	NC
Cardiovascular – other	Quetiapine	3	15	254	29	355	1.08	0.53, 2.30	NC

CVA = cerebrovascular accident; NC = not calculated; NNH = number needed to harm

In the PCTs, olanzapine and risperidone were statistically associated with increases in appetite/weight (OR 4.69, 95% CI 1.87, 14.14; OR 3.40, 95% CI 1.08, 12.75; respectively) while olanzapine was associated with unspecified anticholinergic events in one study (OR 3.29, 95% CI 1.62, 7.17, NNH = 6). As reported in our 2006 evidence report, the CATIE-AD trial found that patients with dementia who were treated with olanzapine, quetiapine or risperidone averaged a monthly weight gain of 1.0, 0.7 and 0.4 pounds while on treatment, compared with a weight loss among placebo-treated patients of 0.9 pounds per month.

Table 23 displays our current analyses on neurological side effects. Aripiprazole, olanzapine, quetiapine, and risperidone were each associated with sedation in dementia patients. The NNH ranged from 7 to 10. Each of these drugs was also statistically associated with an increase in fatigue; NNH ranged from 18 to 21 (not shown). To analyze EPS, we were able to pool four PCTs of aripiprazole, five PCTs of risperidone, and three of quetiapine. Risperidone was associated with an increase in EPS compared with placebo; the NNH was 20, while the odds ratio was 3.00. In the one PCT of olanzapine which reported EPS, subjects in the drug group were more likely to report these symptoms (odds ratio of 15.21, NNH=10). A recent publication from the CATIE-AD trial reported cognitive decline in elderly dementia patients treated with olanzapine, quetiapine, or risperidone²⁷⁹ (not shown).

Table 23. Neurological adverse events among dementia patients—atypical antipsychotics compared with placebo

Adverse Events	Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
		# of studies	# adverse events	sample size	# adverse events	sample size			
Neuro/Sedation	Aripiprazole	4	22	374	116	706	2.62	1.57, 4.54	16
Neuro/Sedation	Olanzapine	5	25	440	158	778	4.58	2.87, 7.55	9
Neuro/Sedation	Quetiapine	4	18	353	84	446	5.16	2.93, 9.51	8
Neuro/Sedation	Risperidone	6	102	922	265	1260	2.33	1.79, 3.05	10
Neuro/Movement Disorder/EPS	Aripiprazole	4	16	374	39	706	1.29	0.68, 2.57	NC
Neuro/Movement Disorder/EPS	Olanzapine	1	2	142	18	100	15.21	3.50, 138.55	10
Neuro/Movement Disorder/EPS	Quetiapine	3	9	254	18	355	1.15	0.46, 3.08	NC
Neuro/Movement Disorder/EPS	Risperidone	5	31	916	130	1561	3.00	1.96, 4.70	20
Neuro/Movement Disorder/Gait	Olanzapine	4	15	373	79	641	2.75	1.52, 5.79	21
Neuro/Movement Disorder/Gait	Aripiprazole	1	1	121	16	366	5.47	0.83, 231.93	NC
Neuro/Movement Disorder/Gait	Quetiapine	3	6	333	18	426	2.36	0.85, 7.59	NC
Neuro/Movement Disorder/Gait	Risperidone	3	8	406	32	448	3.04	1.32, 7.84	33

CI = confidence interval; EPS = extrapyramidal symptoms; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Our expert panel reported cases of diabetes onset in elderly patients taking atypicals; thus, we were encouraged to conduct an analysis on endocrine outcomes. Only one trial, of risperidone, reported this category of adverse events; there was no difference between patients taking the drug and those taking placebo, although the confidence intervals are wide. Results are displayed in Table 24 below.

Table 24. Endocrine adverse events among dementia patients – atypical antipsychotics compared with placebo

Adverse Events	Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
		# of Studies	# Adverse Events	Sample Size	# Adverse Events	Sample Size			
Diabetes	Risperidone	1	5	238	4	235	0.81	0.16, 3.80	NC
Prolactin	Risperidone	1	0	238	0	235	NC	NC	NC

CI = confidence interval; NC = not calculated; NNH = number needed to harm; OR = odds ratio

As displayed in Table 25, urinary symptoms were significantly more common in dementia patients treated with olanzapine, quetiapine, and risperidone than with placebo; NNH ranged from 16 to 36. Confidence intervals were very wide for olanzapine.

Table 25. Urinary symptoms among dementia patients—atypical antipsychotics compared with placebo

Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
	# of Studies	# Adverse Events	Sample Size	# Adverse Events	Sample Size			
Aripiprazole	3	44	348	115	603	1.37	0.92, 2.09	NC
Olanzapine	1	1	94	19	204	9.51	1.47, 401.07	36
Quetiapine	2	12	191	44	332	2.37	1.16, 5.15	16
Risperidone	4	71	665	164	1060	1.55	1.13, 2.13	21

CI = confidence interval; NC = not calculated; NNH = number needed to harm; OR = odds ratio

We found six head-to-head trials of atypicals for dementia that reported adverse events, including the CATIE-AD trial mentioned earlier. Subjects taking olanzapine had greater odds of having a neurological symptom such as “confusion,” “dizziness,” “headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” or “tinnitus” than those taking risperidone (OR 1.54, 95% CI 1.02, 2.34). There also was a trend toward greater odds of sedation with olanzapine (OR 1.40, 95% CI 0.96, 2.05) and quetiapine (OR 1.93, 95% CI 0.97, 3.97) than risperidone, but the results do not meet traditional levels of statistical significance. In one head-to-head trial, a risperidone subject reported a pulmonary adverse event, compared with no subjects in the olanzapine group. In one trial of risperidone versus quetiapine, five of the 34 risperidone subjects reported musculoskeletal problems, compared with none of the 38 quetiapine patients.

We found one new trial comparing adverse events in elderly patients taking either risperidone or SSRIs for depression. There was no difference in adverse events. As reported in our 2006 evidence review, one trial of olanzapine versus benzodiazepines in 205 patients also showed no significant difference in adverse events.

Data from cohort studies. There were also twelve large high-quality cohort studies that reported adverse effects occurring within elderly population taking atypicals for symptoms of dementia; they are displayed in Table 26. Six examined mortality. Populations ranged in size from 9,700 to over 37,000. All were conducted in the United States or Canada. The first found an increased risk of death with atypical antipsychotic use, compared with not using antipsychotics. However, the risk of death with conventional antipsychotics was greater than that with atypicals.⁶⁸ Another study found that patients taking atypicals had a similar adjusted mortality risk to those taking conventional antipsychotics. Both types of antipsychotics had a higher mortality risk than that associated with taking a no antipsychotics.²⁸⁰ A more recent study found that those exposed to haloperidol, olanzapine, or risperidone had a higher risk of death than those not taking any antipsychotics. This study did not find an increased risk of death with the use of quetiapine.²⁸¹ These findings echo another study that found the greatest increase in mortality occurring in those who took higher than the median dose. However, the dosage risk was for conventional antipsychotic therapy. The authors found that the risk of death was higher with conventional versus atypical antipsychotics and the highest risk was during the first 40 days after starting the drug therapy.⁶⁷

Two studies followed new users of antipsychotic medications in nursing home residents^{282,283} over 6 months. Both found a higher rate of death for users of conventional antipsychotics compared with users of atypicals. There were also two studies that examined the risk of stroke

with antipsychotic medications in older individuals. Both combined atypical and conventional antipsychotics as one group. One found the risk of stroke to be 12.4 times as high within the first month of antipsychotic use as not using an antipsychotic, but this risk decreased to mostly insignificant during the following months.²⁸⁴ The other found that hospitalization was increased in the first week after initiation of a conventional antipsychotic but did not find an increased risk of stroke after the initiation of an atypical agent.²⁸⁵ Finally, one study looked at venous thromboembolism (including pulmonary embolus and deep vein thrombosis) across all ages. For those age 65 and older, there were 10 excess cases of venous thromboembolism per year per 10,000 treated with an antipsychotic (either atypical or conventional) compared with four excess cases in those younger than 65.²⁸⁶

Table 26. Adverse events in large observational studies of elderly patients

Reference	Sample	Treatment	Outcomes Measured	Findings
Barnett, 2007 ²⁸⁷	n= 14,029 >65 yo with dementia Data per Veterans Administration and Medicare databases Followed 18 months (2002-2003)	olanzapine, risperidone, quetiapine Or conventional agents	Inpatient admission with a primary or principal diagnosis of cerebrovascular event (CVE) as identified by ICD-9-CM codes from administrative data	CVE risk did not differ in users of atypicals, conventionals or no antipsychotic
Gill, 2007 ⁶⁸	n= 27,259 propensity score-matched pairs Ontario, Canada residents >66 yo dementia per Ontario Health Insurance Plan or Discharge Abstract Database 4/1/97-3/31/02. Community dwelling and long-term care	New users of antipsychotics per Ontario Drug Benefit program after cohort entry atypicals: olanzapine, quetiapine, risperidone Or conventional agents	All-cause mortality as recorded in the Registered Persons Database or the Discharge Abstract Database	New use of atypical antipsychotic associated with statistically significant increase in the risk of death compared with nonuse (community dwelling- adjusted hazard ratio, 1.31 [95% CI, 1.02-1.7]; absolute risk difference 0.2 percentage point. Long-term care 1.55 [CI, 1.15-2.07]; 1.2 percentage points) Conventional antipsychotic use associated with higher risk of death than use of atypicals
Huybrechts, 2011 ²⁸³	n=10,900 British Columbia nursing home patients 1996-2006	Atypical antipsychotics Or conventional agents Or benzodiazepines Or antidepressants	Death and rates of hospital admission within 180 days after treatment initiation	Risk of death associated with conventional antipsychotics, antidepressants and benzodiazepines are comparable or greater than that for atypical antipsychotics.
Kales, 2007 ²⁸⁰	n= 10,615 patients US residents >65 yo dementia per Department of Veteran Affairs national data 2001-2005 outpatient	New users of psychiatric medication after cohort entry atypicals: aripiprazole, clozapine, quetiapine, risperidone, ziprasidone Or conventional agents	12 month mortality rates	Higher mortality rates in users of antipsychotics than nonantipsychotics (22.6-29.1% vs 14.6%) No significant difference in mortality rates between users of atypical vs conventional antipsychotics

Table 26. Adverse events in large observational studies of elderly patients (continued)

Reference	Sample	Treatment	Outcomes Measured	Findings
Liperoti, 2009 ²⁸²	n= 9,729 >65 yo with dementia Data per Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) 1998-2000	New users of antipsychotics In Medicare or Medicaid certified nursing homes in Kansas, Maine, Mississippi, Ohio, South Dakota risperidone, olanzapine, quetiapine, clozapine Or conventional agents	All-cause mortality	Higher rate of death in users of conventional vs atypical agents (hazard ratio 1.26; 95% CI, 1.13-1.42)
Lipkovich, 2007 ²⁸⁸	n= 1,267 >65 yo with dementia and behavioral disturbances Data per olanzapine clinical trial database	olanzapine	Weight change patterns after 20 weeks of treatment	Estimated probability of gaining more than 7% of initial body weight was significantly greater with olanzapine vs placebo (P< .001)
Micca, 2006 ²⁸⁹	n= 1,398 >65 yo with dementia Data per olanzapine clinical trial database	olanzapine	Treatment-emergent diabetes (TED): defined as 2 casual glucose values >200mg/dL at any time after baseline or 1 casual glucose >200mg/dL at the final visit, initiation of antidiabetic medication or new clinical diagnosis of diabetes.	Antipsychotic treatment was not significantly associated with increased risk of TED (HR=1.36)
Pratt, 2010 ²⁸⁵	n= 10,638 (of which 514 were initiated on typical and 564 on atypical antipsychotic) >65, hospitalized for stroke Self-controlled case series, 4 year period from 1/1/03-12/31/06 Australian Government Dept of Veterans' Affairs administrative claims dataset.	Atypical antipsychotics Or conventional agents	Risk of hospitalization for stroke	Hospitalization for stroke was increased in the first week after initiation of conventional antipsychotics (IRR 2.3; 95% CI 1.3, 3.8). No evidence for increased risk of hospitalization for stroke after initiation of atypical.

Table 26. Adverse events in large observational studies of elderly patients (continued)

Reference	Sample	Treatment	Outcomes Measured	Findings
Rochon, 2008 ²⁹⁰	n= 20,682 community dwelling and 20,559 nursing home dwelling >66 yo with dementia Data per Ontario, Canada administrative health care data 30 day f/u between 4/1/97- 3/31/04	olanzapine, quetiapine, risperidone Or conventional agents	Any serious adverse event as defined by the International Conference on Harmonization Clinical Safety Data Management: Definitions and Standards for Expedited Reporting guidelines (i.e.- results in death, is life-threatening, requires inpatient hospital admission or prolongation of existing hospital stay, or results in persistent or significant disability/incapacity)	Compared with patients not using antipsychotics, users of atypicals were 3.2 times more likely (95% CI, 2.77-3.68) to develop a serious adverse event whereas users of conventionals were 3.8 times more likely (95% CI, 3.31-4.39)
Rossom, 2010 ²⁸¹	n= 18,127 5 year retrospective study of veterans national healthcare data Predominantly male, > 65 Dementia 10/99 – 9/05	olanzapine, quetiapine, risperidone Or haloperidol	Mortality during antipsychotic use	Compared with controls not using antipsychotics, during the first 30 days of use, a greater percentage of those exposed to haloperidol (5.4% vs 1.7%, unadjusted HR= 1.4), olanzapine (2.7% vs 1.7%, unadjusted HR=1.6), or risperidone (2.8% vs 2.0%, unadjusted HR=1.4) died. There was no difference between deaths among quetiapine users and controls (1.7% vs 1.7%, unadjusted HR=1.4) and deaths were not greater after the initial 30-day period in any of the cohorts exposed to antipsychotics.
Sacchetti, 2010 ²⁸⁴	n=128,308 >50 years old Health Search Database, Primary Care Patients, Italy	Antipsychotics (does not specify conventional vs atypical)	Time to first ever stroke in elderly primary care people	The cumulative proportion surviving (free from stroke) at the end of the first month was 0.9921 (95% CI 0.9899-0.9943) in subjects exposed to antipsychotics and 0.9995 (95% CI 0.9979-0.9983) in unexposed. At 6 months, figures were 0.9819 (95% CI 0.9761-0.9879) in exposed and 0.9964 (95% CI 0.9960-0.9968) in unexposed. Overall, the risk of stroke was 12.4 times higher in antipsychotic users in the first month but decreased to mostly insignificant within the following months.

Table 26. Adverse events in large observational studies of elderly patients (continued)

Reference	Sample	Treatment	Outcomes Measured	Findings
Schneeweiss, 2007 ⁶⁷	n= 37,241 users of antipsychotics >65 yo British Columbia Ministry of Health data 1/1/96- 12/31/04	Per PharmaNet Database risperidone, quetiapine, olanzapine, clozapine Or conventional agents	All-cause mortality per BC Vital Statistics Agency	Risk of death was comparable and possibly greater with conventional (14.1% died) compared with atypical agents (9.6% died). Mortality ratio 1.47, 95% CI 1.39-1.56

CI = confidence interval; CVE = cerebrovascular event; HR = hazard ratio; SAGE = Systematic Assessment of Geriatric Drug Use via Epidemiology; TED = treatment-emergent diabetes

Other cohort studies focused on diabetes, weight gain, cerebrovascular events, and any serious event, in general. Regarding diabetes, one industry-sponsored and conducted study focused specifically on elderly subjects enrolled in olanzapine trials and found that the risk of diabetes was elevated (hazard ratio = 1.36) but this association was not statistically significant. These authors concluded that the risk of diabetes was more dependent on having an elevated glucose at baseline.²⁸⁹

A cohort study of mostly underweight or normal weight patients with dementia found a greater probability of gaining weight with olanzapine versus other agents, particularly if their BMI was less than 25 at baseline.²⁸⁸

A large study evaluating information from the Veterans Affairs and Medicare databases observed patients with dementia who used antipsychotics over an 18-month period. They found no difference between risk of cerebrovascular event by whether the patient used a conventional, atypical, or no antipsychotic therapy. The only altered risk was in patients with the vascular dementia subtype who received risperidone. They had a decreased risk of cerebrovascular event compared with haloperidol, whereas olanzapine and quetiapine did not.²⁸⁷

One study examined serious adverse events among older adults with dementia living in the community versus in a nursing home. Researchers monitored for any event that resulted in death, was life threatening, required an inpatient hospital admission or prolongation of an existing hospital stay, or resulted in persistent or significant disability incapacity. Patients receiving either an atypical or conventional antipsychotic agent were more than three times more likely to develop a serious event during the 30 days of followup.²⁹⁰

Children/adolescents with ADHD or Tourette's syndrome. Our 2006 CER did not include studies of ADHD. Instead, our 2006 analyses of adverse events in children and adolescents included studies of Tourette's syndrome and autism. Autism is beyond the scope of the current report; thus, those trials are not included in the current analysis.

Data from trials. Our adverse events analyses for Tourette's syndrome and ADHD patients included four PCTs. There were no trials of olanzapine or quetiapine in this population, nor were there any head-to-head trials of atypicals.

Results showed several differences between atypical antipsychotics and placebo. In two trials of risperidone, no placebo patients gained weight, compared with eight of 28 patients on the drug. In another small trial, 32.0 percent of patients on aripiprazole reported EPS, compared with 83.3 percent of placebo patients. The one PCT of ziprasidone had only 28 patients; there were no significant difference in adverse events between groups. Of note, these trials were in general of modest duration, from 4 to 6 weeks.

We found one small trial of clonidine versus risperidone; there were no significant differences in adverse events. We also found 1 trial of haloperidol versus risperidone; 7 of the 24 patients on the conventional antipsychotic reported sleep problems, compared with only 1 of the 26 patients on risperidone.

Data from cohort studies. We did not identify any cohorts of sample sizes of 1,000 patients or greater for the conditions of ADHD or Tourette's syndrome.

Other conditions. Data from trials: Our final adverse events analysis combined trials for anxiety, eating disorders, depression, OCD, PTSD, personality disorders, insomnia, and

substance abuse. As displayed in Table 27, in the PCTs, aripiprazole, olanzapine, quetiapine, and risperidone were each statistically associated with increases in appetite/weight gain (OR 4.18, 11.30, 2.71, and 3.78, respectively) compared with placebo, with olanzapine having the largest association by more than a factor of two. Ziprasidone was not significantly associated with weight gain in two trials.

Table 27. Appetite or weight increase in other conditions—atypical antipsychotics compared with placebo

Drug	# of Studies	Placebo		Intervention Groups		Pooled OR	95% CI	NNH
		# Adverse Events	Sample Size	# Adverse Events	Sample Size			
Aripiprazole	4	8	686	35	701	4.18	1.88, 10.56	35
Olanzapine	11	103	819	382	818	11.30	8.22, 15.74	3
Quetiapine	13	90	1846	279	2887	2.71	2.07, 3.58	16
Risperidone	4	5	197	24	237	3.78	1.35, 13.09	21
Ziprasidone	2	2	113	5	251	1.24	0.19, 13.59	NC

CI = confidence interval; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Death were reported only in two trials of quetiapine; there was no difference between drug and placebo groups. No studies reported CVA. The only significant difference in cardiovascular symptoms between atypicals and placebo involved blood pressure changes in patients taking quetiapine. Strangely, the drug was associated with both decrease (OR 2.01, 95 percent CI 1.25, 3.30) and increase (OR 1.71, 95 percent CI 1.22, 2.39) in blood pressure, casting doubt on this being a causal relationship.

As displayed in Table 28 below, we conducted a meta-analysis on metabolic outcomes, as experts informed us of recent reports of increases in diabetes rates among some patients taking certain atypicals. Results should be interpreted with caution, as we found only one study each of quetiapine, risperidone, and ziprasidone that reported endocrine abnormalities. The risperidone and ziprasidone groups were very small, and only one or two subjects, respectively, had endocrine abnormalities, as compared with no one in either placebo group. “Endocrine abnormalities” in this analysis were a collection of endocrine events other than diabetes (which is reported separately in Table 28), including laboratory abnormalities such as hyperprolactinemia, elevated thyroid stimulating hormone levels, and hypothyroidism, as well as clinical findings commonly due to endocrine abnormalities, such as gynecomastia and amenorrhea. Regarding quetiapine, 5 of the 298 subjects had endocrine adverse events, compared with only 1 of 148 subjects in the placebo group. In two PCTs of olanzapine, the drug was significantly associated with endocrine adverse events (OR 2.37, 95% CI 1.18, 4.94).

Six PCTs of quetiapine reported diabetes outcomes; the pooled odds ratio was elevated at 1.47 but this was not statistically significant compared with placebo. In the one PCT of olanzapine that reported diabetes, 5 of the 370 intervention patients became diabetic, compared with only one of the 377 patients taking placebo, an odds ratio of 5.14, but this was not statistically significant, with very wide confidence intervals (0.6 to 244). In our analysis of three quetiapine PCTs that reported metabolic lab abnormalities (clinically important increases in triglycerides), they were more common in patients taking the drug than those taking placebo (OR 2.20, 95% CI 1.43, 3.47).

Table 28. Endocrine and other metabolic lab abnormalities in other conditions—atypical antipsychotics compared with placebo

Adverse Events	Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
		# of Studies	# Adverse Events	Sample Size	# Adverse Events	Sample Size			
Endocrine	Olanzapine	2	15	190	31	184	2.37	1.18, 4.94	12
Endocrine	Quetiapine	1	1	148	5	298	2.50	0.28, 119.45	NC
Endocrine	Risperidone	1	0	12	1	19	NA	NA	NC
Endocrine	Ziprasidone	1	0	30	2	30	NA	NA	NC
Diabetes	Olanzapine	1	1	377	5	370	5.14	0.57, 244.28	NC
Diabetes	Quetiapine	6	11	1073	32	1753	1.47	0.71, 3.28	NC
Prolactin	Risperidone	1	0	10	1	15	NA	NA	NC
Metabolic lab abnormality	Quetiapine	3	32	537	108	903	2.20	1.43, 3.47	18

CI = confidence interval; NA = not available; NC = not calculated; NNH = number needed to harm; OR = odds ratio

As displayed in Table 29, olanzapine, quetiapine, and ziprasidone were associated with an increase in at least some symptoms categorized as neurological (“confusion,” “dizziness,” “headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” and “tinnitus”) when compared with placebo. All drugs but risperidone were statistically associated with increased fatigue compared with placebo. NNH ranged from 14 to 19. Aripiprazole was associated with increased odds of akathisia (OR 11.78, 95% CI 7.40, 19.61), while the other drugs were not. Aripiprazole, quetiapine, and ziprasidone were associated with increased odds of EPS. NNH was 11 for aripiprazole, 36 for quetiapine and 24 for ziprasidone. All atypicals were associated with increased odds of sedation. NNH ranged from three for quetiapine to 11 for risperidone.

Table 29. Neurological adverse events in other conditions—atypical antipsychotics compared with placebo

Adverse Events	Drug	Placebo			Intervention Groups		Pooled OR	95% CI	NNH
		# of Studies	# Adverse Events	Sample Size	# Adverse Events	Sample Size			
Neuro	Aripiprazole	6	127	795	111	805	0.83	0.62, 1.12	NC
Neuro	Olanzapine	8	56	377	74	369	1.55	1.00, 2.42	17
Neuro	Quetiapine	19	508	2305	881	3,551	1.24	1.09, 1.43	22
Neuro	Risperidone	6	63	261	54	301	0.72	0.45, 1.15	NC
Neuro	Ziprasidone	5	18	212	58	404	1.95	1.06, 3.72	16
Fatigue	Aripiprazole	4	31	686	82	701	2.86	1.83, 4.55	15
Fatigue	Olanzapine	7	43	737	80	720	2.06	1.37, 3.12	19
Fatigue	Quetiapine	13	74	2010	289	3072	2.94	2.20, 3.97	18
Fatigue	Risperidone	4	9	233	9	274	0.83	0.28, 2.41	NC
Fatigue	Ziprasidone	2	0	69	8	111	NA	NA	14
Akathisia	Aripiprazole	5	24	769	190	779	11.78	7.40, 19.61	7
Akathisia	Olanzapine	1	7	25	9	23	2.04	0.50, 8.92	NC
Akathisia	Quetiapine	4	5	488	10	632	1.31	0.38, 5.07	NC
Akathisia	Risperidone	1	0	18	1	19	NA	NA	NC
Akathisia	Ziprasidone	3	9	161	36	321	2.11	0.96, 5.15	NC
EPS	Aripiprazole	5	43	605	99	610	2.75	1.83, 4.19	11
EPS	Olanzapine	3	18	65	17	71	0.87	0.25, 2.97	NC
EPS	Quetiapine	7	35	1100	87	1466	2.62	1.72, 4.06	36
EPS	Risperidone	1	1	10	0	15	0.00	0.00, 26.00	NC
EPS	Ziprasidone	3	6	161	28	321	3.12	1.15, 10.62	24
Sedation	Aripiprazole	7	73	810	160	820	3.03	2.15, 4.32	8
Sedation	Olanzapine	14	127	904	279	901	2.95	2.29, 3.82	6
Sedation	Quetiapine	18	373	2285	1668	3531	5.54	4.78, 6.43	3
Sedation	Risperidone	8	25	290	54	336	2.43	1.39, 4.34	11
Sedation	Ziprasidone	5	21	212	95	392	3.90	2.15, 7.44	6

CI = confidence interval; EPS = extrapyramidal symptoms; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Patients taking atypicals other than aripiprazole had greater odds of decreased salivation (dry mouth) than patients taking placebo. NNH ranged from 7 for quetiapine to 25 for ziprasidone (not shown).

Regarding adults aged 18 to 65, we found one head-to-head trial of olanzapine versus ziprasidone and two head-to-head trials comparing quetiapine to risperidone. Olanzapine was associated with higher odds of weight gain (OR 4.02, 95% CI 2.25, 7.48) when compared with ziprasidone. When compared with risperidone, quetiapine had higher odds of decreased salivation, neurological events, sedation, and agitation.

There were two trials of olanzapine versus a mood stabilizer. Olanzapine patients had lower odds of gastrointestinal side effects, low platelet count and mania. Olanzapine patients had higher odds of weight gain, dry mouth, liver function test abnormality, EPS, sedation, speech disorder, and depression. We found one small trial of quetiapine versus a mood stabilizer: the only difference in adverse effects (AEs) involved EPS, with quetiapine patients less likely to experience them.

A handful of trials compared AEs between an atypical antipsychotic arm and an SSRI arm. Olanzapine and quetiapine patients had greater odds of weight gain than placebo patients, while risperidone patients did not. Olanzapine and risperidone patients also had higher odds of cardiac events. Olanzapine, quetiapine and ziprasidone patients had higher odds of dry mouth, while risperidone patients did not. Although there was no difference in diabetes rates, higher rates of metabolic lab abnormalities were reported in one trial of quetiapine versus SSRI. Fatigue was

more common in olanzapine, quetiapine, and ziprasidone than in SSRIs, and sedation was more common in olanzapine and quetiapine patients.

We were able to compare adverse events in conventional versus atypical antipsychotics in four trials of olanzapine and one of aripiprazole. Weight gain was more common among both olanzapine and aripiprazole patients than those taking conventional antipsychotics (OR 2.72 and 1.61 respectively). In one trial, olanzapine patients were less likely to observe cardiovascular symptoms, fever/infection, gastrointestinal, and musculoskeletal problems. In four pooled trials of olanzapine, patients were less likely (OR 0.28, 95% CI 0.23, 0.33) to experience EPS than patients on conventional antipsychotics. In one trial of aripiprazole versus conventional antipsychotics, fewer aripiprazole patients experienced akathisia (OR 0.44, 95% CI 0.33, 0.60) and EPS (OR 0.24, 95% CI 0.18, 0.32).

Schizophrenia. Because of the paucity of head-to-head data directly comparing adverse events among atypical antipsychotics prescribed for off-label uses in the non-elderly, we reviewed the results of the CATIE trial, a multicenter study at 57 U.S. sites that randomized 1,493 patients with schizophrenia (the indicated condition for these drugs) to receive either olanzapine, quetiapine, risperidone, ziprasidone, or the conventional antipsychotic perphenazine. This study found that risperidone had the lowest rate of treatment discontinuation due to intolerable side effects (10 percent), whereas olanzapine had the highest rate (18 percent). More patients treated with perphenazine discontinued treatment due to extrapyramidal effects than did those treated with any of the atypical antipsychotics (8 percent vs. 2–4 percent). However, there were no significant differences among the groups in the incidence of EPS, akathisia, or movement disorders, as measured by the AIMS Global Severity Score, the Barnes Akathisia Rating Scale, or the Simpson-Angus Extrapyramidal Signs Scale. Weight gain was more common in patients treated with olanzapine (average weight gain of 2 lbs. per month) than in other patients. Two to three times as many patients in the olanzapine-treated group gained 7 percent or more of their baseline body weight as those in the other groups. More patients discontinued therapy with olanzapine due to weight gain or metabolic effects than those treated with other drugs (9 percent vs. 1–4 percent). Adverse changes in glycosylated hemoglobin, cholesterol, and triglycerides were also more likely in olanzapine-treated patients than in those treated with the other drugs, while changes in blood glucose level were also greater in olanzapine-treated patients, but the difference did not reach statistical significance. Only risperidone was associated with increasing prolactin levels. Quetiapine treated patients had higher rates of anticholinergic effects (such as dry mouth) than the other drugs, whereas patients treated with olanzapine or quetiapine had lower rates of insomnia than did patients in the other groups. Although the CATIE trial has been criticized for the dropout rate and the perception that the dose of olanzapine used was comparatively higher than the dose for the other atypical antipsychotics, these data support the findings from the clinical trials of atypical antipsychotics for off-label indications that olanzapine causes the most weight gain but is associated with lower rates of insomnia and that treatment with atypical antipsychotics results in fewer EPS and movement disorders than does treatment with conventional antipsychotics.

Data from cohort studies. As reported in our original evidence report, one large observational study reported lower odds of diabetes in risperidone subjects than in placebo subjects (OR= 0.21, 95% CI 0.07, 0.51).

One new cohort study investigated the risk of hyperlipidemia with antipsychotic treatment of depression. Treatment with risperidone, quetiapine, olanzapine and ziprasidone, but not aripiprazole, caused a significant increase in the risk of incident hyperlipidemia.²⁹¹ One study of sudden cardiac death in patients aged 30 to 74 found that users of either conventional or atypical antipsychotics had a similar, dose-related increase compared with nonusers.²⁹²

Discussion

In summary, there is consistent high strength evidence across multiple trials that olanzapine is associated with more weight gain than placebo, conventional antipsychotics, or other atypical antipsychotics. This was a conclusion from our 2006 report; that conclusion is unchanged in this update. Evidence about weight gain for other atypical antipsychotics is not as robust, but stronger in this update than in our earlier report. In nonelderly adults, olanzapine, risperidone, quetiapine and aripiprazole are all statistically significantly associated with weight gain compared with placebo. From limited data, ziprasidone was not associated with weight gain. The association of aripiprazole with weight gain was unexpected by a project psychiatrist.

There is an emerging signal that some atypical antipsychotics are associated with the development of metabolic laboratory abnormalities or overt diabetes. Again, olanzapine stands out from the other drugs with regard to this signal. The strength of evidence for this signal is low, meaning we expect further research to change our confidence in the estimate of the effect and is likely to change the effect.

Although the evidence from off-label use is insufficient to draw conclusions, limited evidence from patients with schizophrenia suggests that atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol. The strength of evidence for this outcome is low. There is moderate strength evidence that olanzapine and risperidone are associated with an increase in extrapyramidal signs or symptoms (excluding tardive dyskinesia) relative to placebo. The CATIE-AD trial also concluded that EPS are more common with olanzapine and risperidone than quetiapine, and that all three drugs are associated with cognitive decline. Quetiapine was associated with EPS in our pooled analysis of seven studies of non-elderly adults; this finding was also surprising and warrants additional investigation. There is low strength evidence that, in nonelderly adults, the atypical antipsychotics aripiprazole and olanzapine are associated with a lower risk of side effects than are conventional antipsychotics.

There is high strength evidence from meta-analyses that the use of atypical antipsychotics is associated with an increased risk of death in elderly patients with dementia and agitation. For risperidone, this outcome may be related to an increased risk of stroke. New since our prior report is stronger evidence that conventional antipsychotics probably also increase the risk of death in similar patients, perhaps to the same or greater degree than atypical antipsychotics; however, the strength of evidence for this outcome is moderate, as data come primarily from high quality observational studies. Further research may change our confidence in the estimate or may change the estimate itself.

Other differences in adverse events/safety between atypical antipsychotics and conventional antipsychotics or placebo were either small or inconsistent. New since our prior report is one exception to this general conclusion: an emerging signal of an increase in urinary symptoms in older adults with dementia taking atypical antipsychotics relative to placebo.

Key Question 5. What is the effective dose and time limit for off-label indications?

Key Points

Dementia trials that included arms with different dosages usually reported a dose-response trend with higher doses resulting in higher efficacy; this trend was not statistically significant.

Our meta-analyses of MDD trials that compared quetiapine dosages found no statistical difference between 150 mg and 300 mg in percent of sample remitting or responding based on the MADRS.

One trial of the treatment of borderline personality disorder with olanzapine demonstrated improvement when 5-10 mg daily was used but no difference from placebo with 2.5 mg dose.

Our meta-analysis of olanzapine for eating disorders found no increase in BMI compared with placebo at either one or three months.

Our meta-analysis of PTSD trials found pooled results from at least 12 weeks followup were not statistically different from those reported at less than 12 weeks.

Detailed Analysis

Dosage. Five of the dementia PCTs contained treatment arms for different doses. There were too few studies to pool dosage results by drug: we found one of aripiprazole,¹⁰⁷ two of olanzapine,^{110,111} one of quetiapine,¹²² and one of risperidone.¹²⁷ Each of these studies reported results per arm for total score agitation scale, and psychosis scales on the BEHAVE-AD, BPRS, or NPI. The results of these trials are displayed on Figures 25, 26, and 27. All but one study of olanzapine¹¹⁰ reported increased efficacy with increased dosage. However, this trend is not statistically significant, as the 95 percent confidence intervals for the treatment arms in each study overlap.

Figure 25. Dementia: PCTs—with dose comparisons—total/global scores

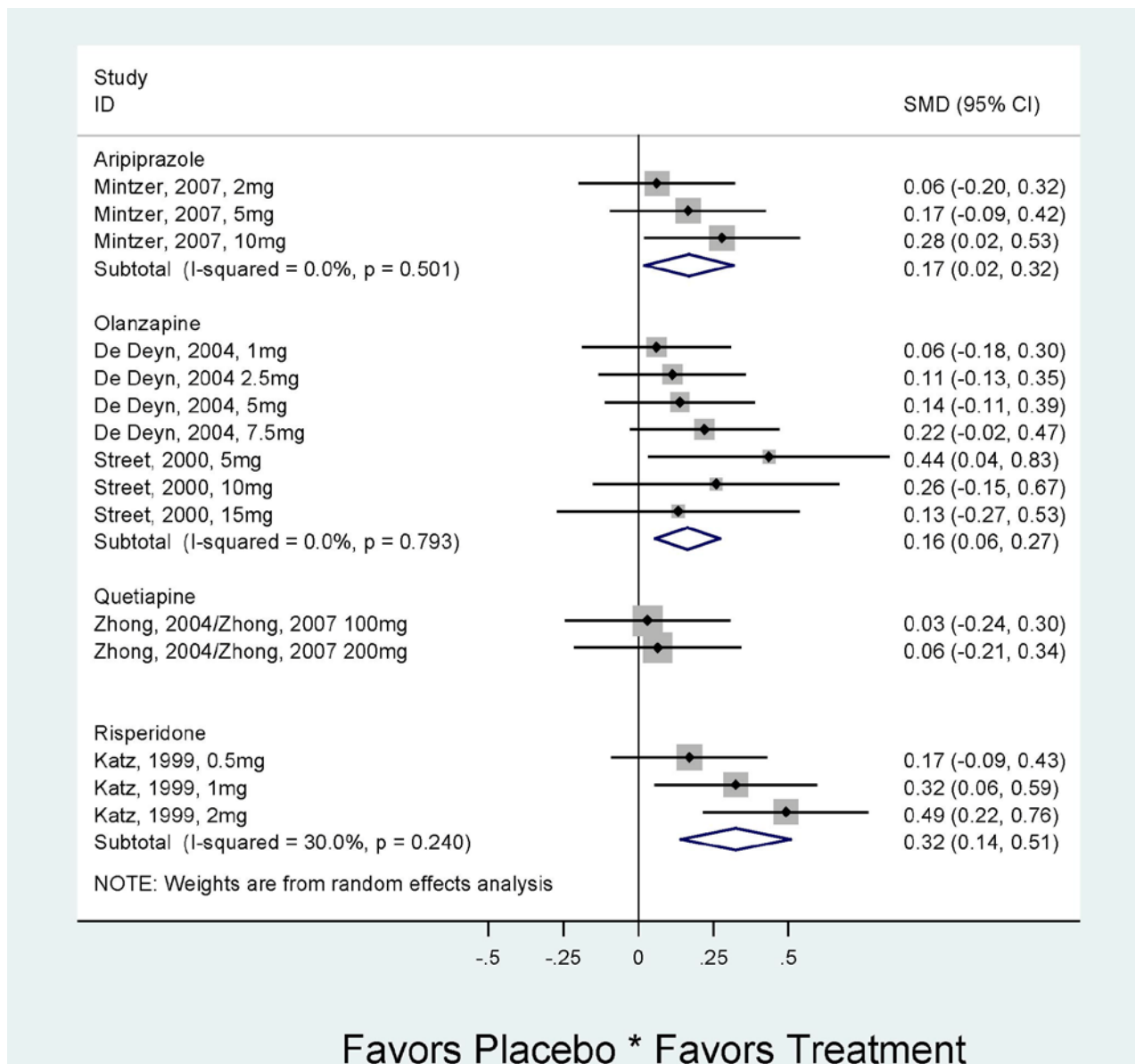


Figure 26. Dementia: PCTs with dose comparisons—psychosis

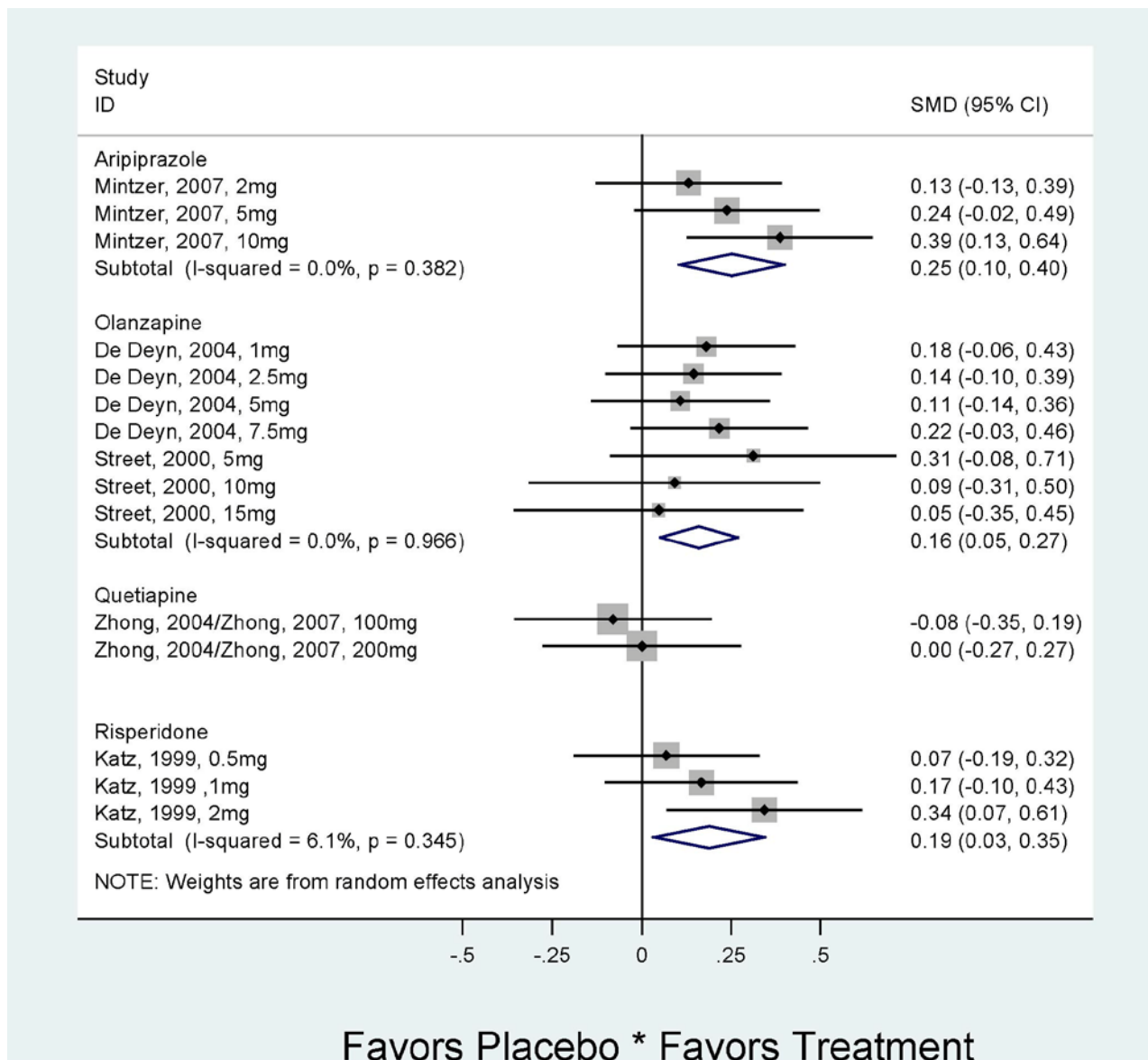
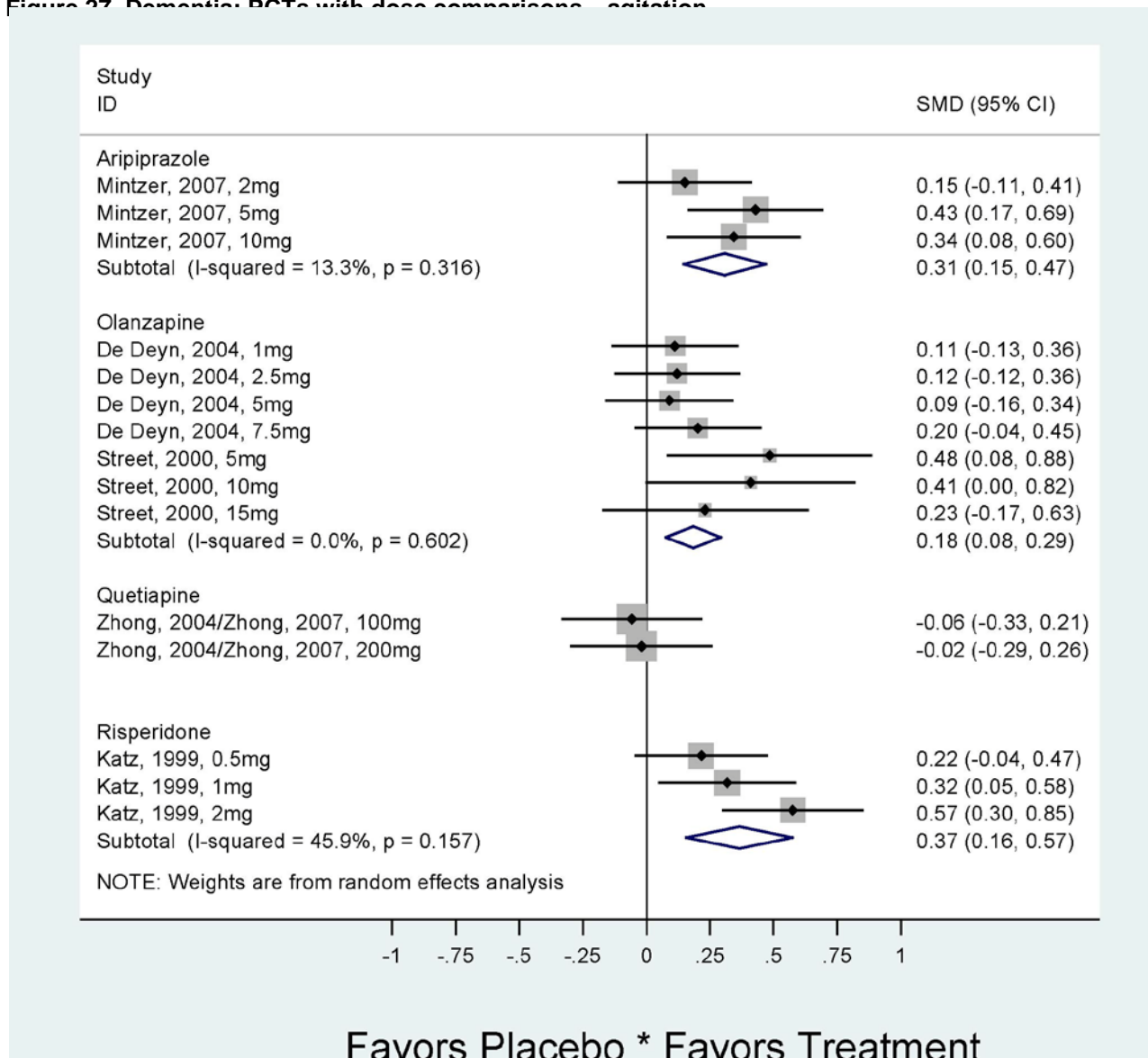


Figure 27. Dementia: PCTs with dose comparisons - agitation



We found four depression PCTs in the nonelderly population that contained treatment arms for different doses.^{159,162,171,172} All studied quetiapine and all contained both 150 mg and 300 mg arms. One also included a 50 mg arm.¹⁷² Results of our meta-analyses are presented in Figures 28 and 29; outcomes were percentage of patients remitted or responded according to the MADRS. (Please see Key Question 2 section for further description of these outcomes.) Though three of the PCTs reported the 300 mg arm slightly superior to the 150 mg arm, the results were not statistically significant. The relative risk (RR) of entering remission, versus patients taking placebo, were 1.36 (95% CI 1.12, 1.64) for patients taking 150 mg and 1.51 (95% CI 1.25, 1.81) for patients taking 300 mg. Patients in the one 50 mg group had RRs of 1.40 (95% CI 0.95, 2.07). The RRs of responding, versus patients taking placebo, were 1.42 (95% CI 1.22, 1.67) for patients taking 150 mg and 1.43 (95% CI 1.25, 1.63) for patients taking 300 mg. Patients in the one 50 mg group had an RR of 1.41 (95% CI 1.07, 1.85).

Figure 28. Depression—MADRS % remitted—dose

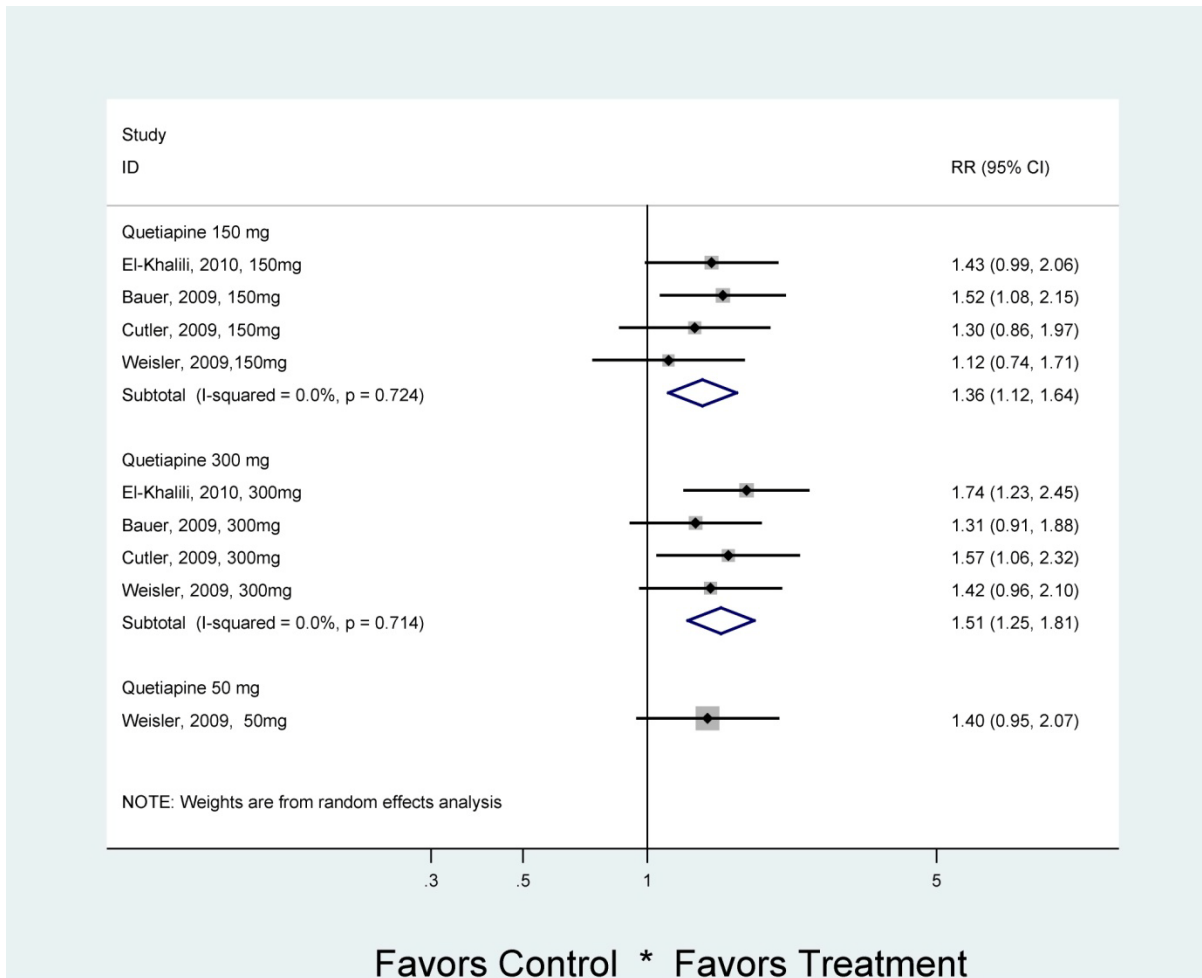
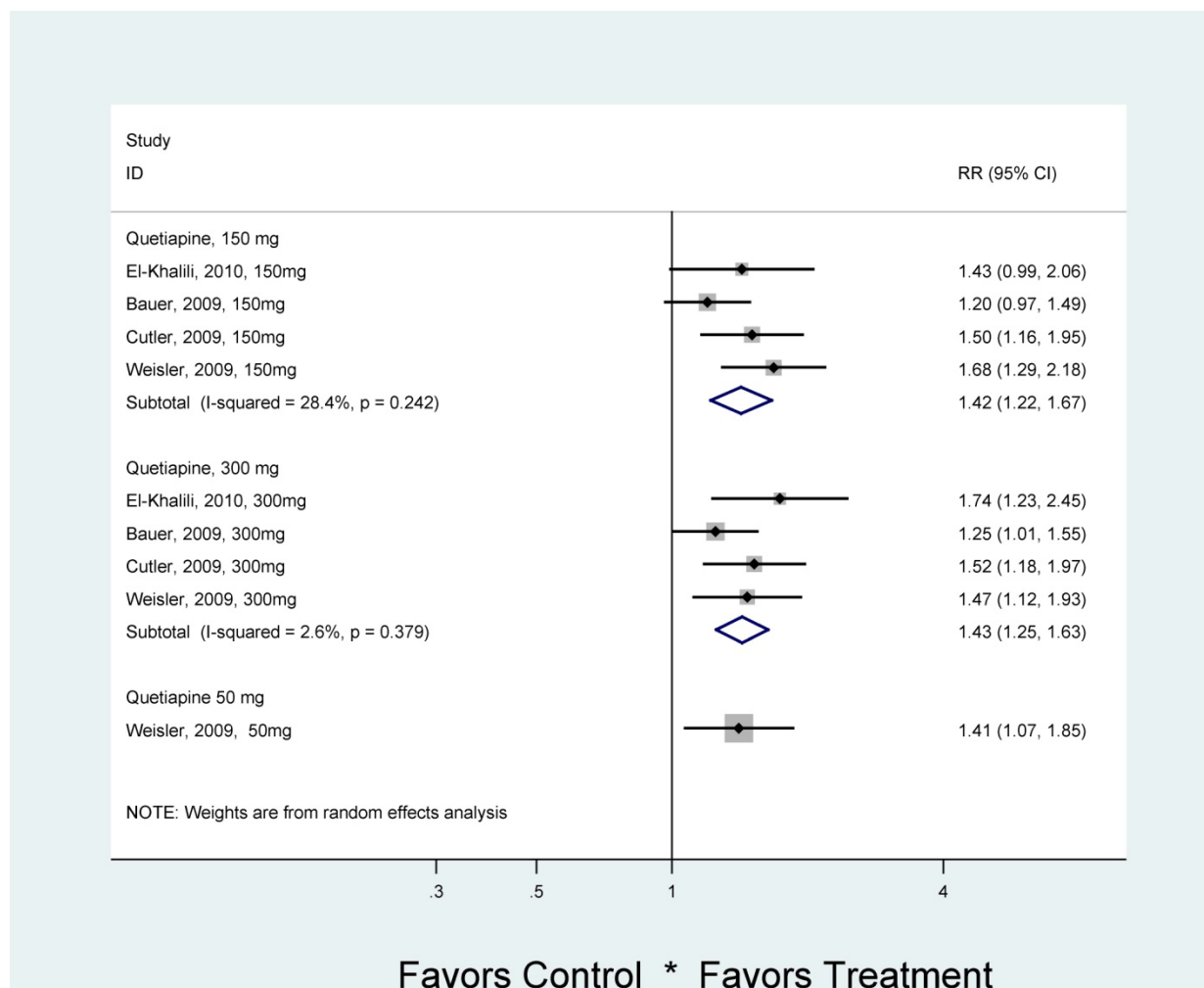


Figure 29. Depression—MADRS % responded—dose



Finally, one trial of borderline personality disorder treatment with olanzapine demonstrated improvement when 5–10 mg was used each day but no difference from placebo when 2.5 mg was used.²²⁰

Timing. There were only enough studies to pool data by duration for PTSD and eating disorders. Forest plots are presented in Figures 20 and 16, respectively, in the results section for Key Question 2. For the PTSD studies, there was no statistically significant improvement in CAPS scores for risperidone treatment over placebo at less than 12 weeks.^{231,234,237} There were only two studies that reported improvement in CAPS scores for greater than 12 weeks, so those data could not be pooled. The one PTSD study that reported outcomes at both greater than and less than 12 weeks found risperidone not significantly different from placebo, regardless of time point.²³⁷

There were three eating disorder trials that measured changes in BMI with use of olanzapine at 1 and 3 months compared with placebo.^{180,182,183} There was no significant improvement, compared with placebo, at either of the time points.

There were two studies of the same population of BPD patients receiving treatment with aripiprazole.^{218,219} The first of these measured the population at 8 weeks and the second at 18 months. Both time points demonstrated improvement in Symptom Checklist 90-revised (SCL-90) scores.

Discussion

For most conditions, there are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum effective dose. Most studies used flexible dosing, with patients on a wide range of doses. From limited data, it appears that 150 mg quetiapine daily augmentation is equally efficacious as augmentation with 300 mg for MDD patients who respond inadequately to SSRIs, as measured by the percentage of remitters and responders according to the MADRS. More trials comparing different doses of other atypicals for depression would help guide clinicians in treating this population. In addition, more dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder would allow for pooling and comparison of results.

Though there is data regarding duration of treatment in PTSD, eating disorders, and BPD, the outcome of treatment appears to be the same regardless of time point.

Summary and Discussion

We conducted an extensive literature search, data abstraction, and meta-analyses, whenever possible, to assess the efficacy, comparative effectiveness, and safety of atypical antipsychotics for off-label indications. Since the submission of our original comparative effectiveness review (CER) in 2006, many new high-quality controlled trials have been published; we were able to add many to our prior quantitative analyses and conduct additional analyses on new conditions and adverse events. In this chapter, we describe the limitations of our review and meta-analyses and then present our conclusions. We also discuss the implications of our findings for future research.

Limitations. Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, the possibility of publication bias still exists. For the most part, our assessment did not yield any evidence of unexplained heterogeneity. Two exceptions include one outcome for depression and the Y-BOCS “percent of participants responded” outcome used in our obsessive-compulsive disorder (OCD) meta-analysis. In our analysis of atypicals as augmentation in treatment of major depressive disorder (MDD), possible publication bias appeared in studies reporting the percent of participants remitted according to the Montgomery-Asberg Depression Rating Scale (MADRS). We conducted additional efficacy meta-analyses using Hamilton Depression Rating Scale (HAM-D) outcomes; efficacy results were similar, but no heterogeneity was detected. Thus, our confidence that some atypicals are efficacious as augmentation of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) for depression remains despite evidence of possible publication bias. Heterogeneity was also evident in studies assessing the efficacy of atypicals for OCD. This heterogeneity was likely due to patient enrollment criteria; studies used different definitions of “refractory” and “treatment resistant.” Another published meta-analysis of atypicals for OCD¹⁹² found similar efficacy results but no heterogeneity according to statistical tests.

Furthermore, when we reviewed the recent meta-analysis assessing death and the use of these drugs in persons with dementia, we learned of the existence of some manufacturer-supported trials, the published results of which we searched for and were not able to find, despite extensive computerized searches and requests to the manufacturers (we have since learned the results were not published). It is possible that other such unpublished trial results exist for the other conditions included in our report. In addition, we excluded non-English language studies. Thus, we assume that publication bias may occur for all conditions, resulting in an overestimation of efficacy of these drugs and conditions.

An important limitation common to systematic reviews is the quality of the original studies included. In order to measure the quality of clinical trials we used the Jadad scale.¹⁷ As empirical evidence regarding other study characteristics and their relationship to bias is lacking, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. In our 2006 CER on off-label use of atypicals, we conducted a sensitivity analysis on the relationship between trial quality and effect size; the better quality trials reported an effect size 25 percent smaller than did lower quality trials. This finding increases the likelihood that a synthesis of results of all studies—whether narrative or quantitative—may produce inflated estimates of efficacy. As stated above, the higher general quality of the dementia and depression augmentation studies led

to a greater strength of evidence rating for those uses. Another factor contributing to our conclusions is the degree to which the available evidence comes from manufacturer-supported studies. In studies of other drugs and in studies of atypical antipsychotic drugs in particular, there is evidence that sponsorship by the manufacturer is more likely to yield results favorable to the manufacturer's product. In some cases this has been related to design or reporting methods that intentionally favor the manufacturer's product. Thus, to the extent that all or almost all of the available evidence supporting drug/indication came from the manufacturer, we downgraded our confidence in the conclusion. The existence of Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD), which was federally sponsored and reported results consistent with the manufacturer supported studies, substantially increases our confidence regarding the studied atypical antipsychotics for elderly patients with dementia.

We could come to very few conclusions regarding dosage. Most trials used flexible dosing, so patients were on a wide range of doses.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals must be known to assess applicability. Such data were reported unevenly in the studies we reviewed. The dementia trials were most often conducted in nursing homes, hospitals, or assisted living facilities. According to our review on utilization patterns, these settings represent where atypicals are most often used in the elderly. Studies for other conditions were not particularly representative. For example, three of the four trials for Attention-Deficit Hyperactivity Disorder (ADHD) were conducted in children with severe co-occurring conditions, such as bipolar disorder or mental retardation.

In the studies of atypicals as augmentation for SSRI or SNRI patients with MDD, it was often unclear whether patients were simultaneously undergoing psychotherapy. One trial¹⁶⁵ specifically stated that subjects were prohibited from initiating such therapy during the trial, but other reports were unclear on the issue. Thus, it is unclear whether treatment over and above the medication influenced the study results. As many depression patients are treated in primary care, it is important to note that subjects in the depression trials were recruited from both primary care and mental health centers.

We found only one controlled trial of atypicals for treatment of insomnia. Among observational studies only one small one¹⁸⁸ included patients with insomnia as primary diagnosis. Others included patients with Parkinson's disease, MDD, polysubstance abuse withdrawal symptoms, and tamoxifen induced insomnia. Thus, the results of these studies should not be applied to the general population.

Conclusions. Tables 30 and 31 present the most clinically relevant findings. It is important to note that we found no trials, large observational studies, or utilization studies of the three newest atypicals (asenapine, iloperidone, and paliperidone) for off-label uses. Table 30 is organized as follows: First, all conditions dealt with in our original CER, in alphabetical order; second, all the new off-label indications in alphabetical order.

Table 30. Summary update: efficacy of atypical antipsychotics for off-label use

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Dementia	High	<p>A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole.</p> <p>There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant.</p> <p>Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.</p>	<p>Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude.</p> <p>Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.</p> <p>Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI.</p> <p>Three head to head trials compared atypicals; none was found superior.</p>	<p>Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.</p>
Depression – MDD: augmentation of SSRI / SNRI	<p>Moderate - risperidone, aripiprazole, quetiapine</p> <p>Low – olanzapine, ziprasidone</p>	<p>Three trials assessed the combination of olanzapine and fluoxetine , one trial each assessed augmentation of various SRIs with risperidone, ziprasidone, and quetiapine, and one study assessed adding risperidone versus olanzapine to SSRI.</p> <p>The combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine.</p> <p>The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.</p>	<p>We conducted a meta-analysis using “response” to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone and ziprasidone were included in two trials and one trial, respectively, these reported the drug superior to placebo.</p> <p>One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.</p>	<p>Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p>

Table 30. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Depression – MDD: Monotherapy	Moderate	The three olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	In our meta-analysis of five placebo controlled trials, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.
Obsessive compulsive disorder – augmentation of SSRI	Moderate – quetiapine, risperidone Low - olanzapine	12 trials used risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy. Relative risk of “responding” significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	Our updated meta-analysis found risperidone superior to placebo, as measured by changed in the Yale Brown Obsessive Compulsive Scale (Y-BOCS). There were too few studies (two) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. One new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Risperidone has efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also have efficacy . Quetiapine is more efficacious than ziprasidone and clomipramine for this purpose.
Obsessive compulsive disorder – augmentation of citalopram	Low- quetiapine Very low - risperidone	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared with placebo (102 days v. 85 days)	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.

Table 30. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Post traumatic stress disorder	Moderate – risperidone Olanzapine – Low Quetiapine – very low	Four trials of risperidone and two trials of olanzapine, each of at least 6 week duration, treated patients with PTSD. Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	Three new trials of risperidone were found, allowing us to conduct a meta-analysis using the Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A new trial found a 3-fold decline in CAPS scores in patients treated with quetiapine monotherapy compared with placebo. Exact scores were not reported. We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.
Personality disorders - borderline	Low – aripiprazole Very low – quetiapine, olanzapine	Three trials provide evidence that olanzapine is superior to placebo & may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Aripiprazole was superior to placebo in one small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared with placebo at 12 weeks. Two new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. One new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Olanzapine had mixed results in 7 trials, aripiprazole was found efficacious in two trials, quetiapine was found efficacious in one trial, and ziprasidone was found not efficacious in one trial.
Personality disorders - schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had mixed results when used to treat schizotypal personality disorder in two small trials.
Tourette's syndrome	Low	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared with placebo.	No additional trials.	Same as 2006: Risperidone is at least as efficacious as pimozide or clonidine for Tourette's syndrome.

Table 30. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Anxiety	Moderate	Not covered.	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine has efficacy as treatment for Generalized Anxiety Disorder
Attention deficit / hyperactivity disorder – no co-occurring disorders	Low	Not covered.	One trial showed risperidone superior to placebo in reducing scores on the Children’s Aggression Scale – Parent version (CAS-P).	Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.
Attention deficit / hyperactivity disorder - mentally retarded children	Low	Not covered.	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.
Attention deficit / hyperactivity disorder - bipolar children	Low	Not covered.	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is inefficacious in reducing ADHD symptoms in children with bipolar disorder.
Eating disorders	Moderate – olanzapine Low - quetiapine	Not covered.	Five trials of olanzapine were found; three reporting Body Mass Index (BMI) could be pooled. There was no difference in change in BMI at either one or three months compared with placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.
Insomnia	Very low.	Not covered.	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be inefficacious in treating insomnia.
Substance abuse - alcohol	Moderate – aripiprazole Low – quetiapine	Not covered.	Two trials of aripiprazole and one of quetiapine reported % of patients completely abstinent during follow-up. In our pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is inefficacious in treating alcohol abuse / dependence. Quetiapine may also be inefficacious .
Substance abuse - cocaine	Low	Not covered.	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is inefficacious in treating cocaine abuse / dependence. Risperidone may also be inefficacious .

Table 30. Summary update: efficacy of atypical antipsychotics for off-label use (continued)

Usage	Strength of Evidence	2006 Findings	2011 Findings	2011 Conclusions
Substance abuse – methamphetamine	Low	Not covered.	One trial found aripiprazole ineffective in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole ineffective in reducing craving for methamphetamine.	Aripiprazole is ineffective in treating methamphetamine abuse/dependence.
Substance abuse – methadone clients	Low	Not covered.	One trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an ineffective adjunct to methadone maintenance.

ADHD = attention-deficit hyperactivity disorder; BEHAVE-AD = Behavioral Pathology in Alzheimer’s Disease Scale; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; CAPS = Clinician-Administered PTSD Scale; CAS-P = Children’s Aggression Scale-Parent Version; CGI-I = Clinical Global Impression Improvement; CGI-S = Clinical Global Impression-Severity; CMAI = Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NPI = Neuropsychiatric Inventory; PANSS = Positive and Negative Syndrome Scale; PCT = placebo-controlled trial; PTSD = post-traumatic stress disorder; SNAP-IV = Swanson, Nolan, and Pelham Rating Scale; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitors; Yale-Brown Obsessive-Compulsive Scale

Table 31. Summary update: safety of atypical antipsychotics for off-label use

Adverse Event	Head to Head Comparisons	Active Comparisons	Placebo Comparisons
Weight gain – Elderly patients	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared with a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone than placebo according to our meta-analysis.
Weight gain – Adults 18 - 64	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Weight gain – Children & adolescents	No head-to-head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality - Elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we can not make conclusions regarding safety here.
Endocrine / diabetes – Elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.

Table 31. Summary update: safety of atypical antipsychotics for off-label use (continued)

Adverse Event	Head to Head Comparisons	Active Comparisons	Placebo Comparisons
Endocrine / diabetes – Adults 18 - 64	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA - Elderly patients	No evidence reported.	Hospitalization for CVA was increased in the first week after initiation of conventional antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
EPS - Elderly patients	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported.	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
EPS – Adults 18 - 64	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to our meta-analysis.
Sedation –Elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant.	No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials of olanzapine and three of risperidone versus conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.
Sedation – Children and adolescents	No head-to-head trials.	No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

Table 31. Summary update: safety of atypical antipsychotics for off-label use (continued)

Adverse Event	Head to Head Comparisons	Active Comparisons	Placebo Comparisons
Sedation – Adults 18-64	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone versus olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in our pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in our meta-analysis.

CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease; CVA = cerebrovascular accident; EPS = extrapyramidal symptoms; PCT = placebo-controlled trial

Future Research

The overarching finding of this review is that although atypical antipsychotic medications are being used for a large number of off-label uses, we were able to find moderate to strong evidence to support efficacy for only a few of the drugs and only a few of the off-label uses. Most of the evidence is concentrated in the drugs risperidone, olanzapine, and quetiapine, and the conditions dementia, depression, and obsessive-compulsive disorder. For the newly approved atypicals (asenapine, iloperidone, and paliperidone), we found no clinical trials assessing their use for any off-label condition, and for some off-label uses, we found no or only a small number of trials. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label uses suggests that efficacy differs between drugs, meaning that the assumption of a “class effect” for atypical antipsychotics may be unwarranted. This means that each drug is going to require its own evaluation of efficacy for each off-label indication, which is a large task; and then drugs demonstrated to be efficacious will need to be tested head-to-head in trials of comparative effectiveness.

With respect to use in individual off-label conditions, we offer the following thoughts.

ADHD. We found three placebo-controlled trials and one active-control trial. Two of these studied risperidone and two studied aripiprazole. Though these did find some efficacy for ADHD, the trials utilized differing outcome measures and the patient populations differed in severity of illness and comorbid conditions. For these reasons, the trials could not be pooled and overall efficacy in ADHD still needs to be established for each medication. Future research should utilize one standard measure of ADHD in order for them to be compared. In addition, we learned from utilization studies that other atypical antipsychotic medications, such as quetiapine and olanzapine are being used frequently for ADHD. As we found no trials of their efficacy, future research should include studies of these medications.

Anxiety. Though there were many placebo-controlled trials of atypicals for anxiety symptoms, only three were clinically similar enough to pool. These trials used quetiapine for generalized anxiety disorder. There were mixed reports of efficacy for the other atypicals and there were no studies of anxiety treatment with aripiprazole. Future research needs to include additional studies of the various atypical agents. As the Hamilton Anxiety Rating Scale (HAM-A) was the most commonly used measure, if these future trials utilized the HAM-A, it will be possible to compare across trials.

Dementia. Given the concern over serious adverse events such as mortality, knowledge of the efficacy of atypical antipsychotics in the demented elderly is of paramount importance. We found evidence that aripiprazole, olanzapine and risperidone were superior to placebo in treating agitation, psychosis, and behavioral symptoms. We found no trials of ziprasidone in dementia. An assessment of the net efficacy compared with the side effect burden would be useful in future studies.

Depression. There were enough trials of quetiapine and risperidone to pool to show efficacy when used as an augmentation agent. Olanzapine augmentation was shown to be superior to placebo but there were only two trials. There was only one placebo-controlled trial of ziprasidone in depression. Though it was found to be superior, further studies to confirm this finding are required.

Eating Disorders. As weight gain is a common side effect experienced during treatment of other conditions with olanzapine, the assumption has been that this side effect could be exploited for therapeutic benefit as a treatment for eating disorders. Though commonly used clinically, the four trials of olanzapine in eating disorders found that it led to no statistically significant difference in body mass index. Mechanistic studies to explain differences in those with eating disorders from those with other psychiatric conditions may elucidate why weight gain occurs in some populations but not others.

Insomnia. Insomnia is another condition where the side effects of atypical antipsychotics are exploited for treatment. Atypicals, particularly olanzapine and quetiapine, are commonly sedating. Clinical trials are needed to rigorously test the conclusions from observational studies that olanzapine and quetiapine are useful in promoting sleep quality and sleep onset. Placebo controlled trials confirming their efficacy are necessary before reaching any conclusions.

OCD. Several trials reported the efficacy of quetiapine as an augmentation agent in OCD along with a few of risperidone. Further studies of olanzapine and aripiprazole are required in order to assess their efficacy. In addition, further trials comparing the atypical antipsychotic agents to the current standards of treatment would be helpful in order to know at which point of treatment failure there benefit is greatest. For example, one trial found that quetiapine had greater efficacy in reducing the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score than clomipramine, though clomipramine is currently a more widely recommended treatment for resistant OCD. If further trials confirmed this result, atypical antipsychotics could be placed higher on an algorithm for recommended treatment.

Personality Disorders. Personality disorders have remained a difficult area for clinicians, leading to continued exploration for successful treatments. Unfortunately, our ability to reach strong conclusions is hindered by the heterogeneity of the trials reviewed. Future research should have standard outcomes so that results across trials can be compared. In our review, olanzapine and risperidone had mixed results, and quetiapine and aripiprazole were found to have some efficacy while ziprasidone did not. However, there were too few trials to allow for clinicians to predict the effect of a particular agent for a particular patient. Before reaching conclusions regarding clinical use further research, with comparable outcomes, is necessary.

Post-Traumatic Stress Disorder. Some studies found efficacy for risperidone, olanzapine and quetiapine for the symptoms of post-traumatic stress disorder (PTSD). An issue in PTSD is the question of whether the results are affected by gender. Our review found that the atypicals showed efficacy in male combat veterans but not female victims of civilian trauma. Whether this signifies that efficacy differs by gender or rather that combat trauma is more amenable to treatment with atypicals than civilian trauma requires further research to elucidate.

Substance Abuse. Trials of atypical antipsychotic treatment for substance abuse did not find them superior to placebo on substance use measures. Future research is needed to establish a role, if any, in the use of atypical antipsychotic drugs in the treatment of substance abuse.

Tourette's Syndrome. Other than efficacy demonstrated with risperidone, there is only one placebo-controlled trial of another atypical antipsychotic, ziprasidone, as a treatment for Tourette's syndrome. Additional trials are needed before any conclusions can be reached regarding the other atypicals.

In addition to the research recommended above, there is almost no evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or other comorbidities. In addition, existing evidence about the effect of baseline severity of disease is too heterogeneous to allow us to draw conclusions. In future research, standardized measures of disease severity might allow for greater knowledge of the patient populations who would benefit from treatment with atypical agents.

Regarding adverse effects of the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event. It would facilitate assessments if future studies contained a standardized list of assessed side effects. As many trials report only those effects observed, we are unable to compare between trials for many of the side effects.

Two of the adverse events deserve further comment, because they potentially differ from the perception of clinical psychiatrists. In four studies including 1,387 nonelderly patients, aripiprazole was associated with weight gain, and in seven studies including 2,566 nonelderly patients quetiapine was associated with extrapyramidal symptoms. We consider these findings to be a signal deserving of further investigation.

Another area where clinical guidance is needed is in the dosages required to achieve effects in off-label indications. The dosages used off-label varied from those used for on-label indications. There were a few trials that compared dosage efficacy, but most used flexible dosing. Thus, a dosage comparison across trials was generally not possible. More research examining differing dosages within the same population is required in order to guide clinicians in the appropriate doses to prescribe. A similar issue is that of treatment length. More research reporting responses at various time points would be helpful in determining how long treatment is required. Given the risk of side effects when using these agents, clinicians need to know when a result is expected to prevent continuing an ineffective agent, unnecessarily.

Newer agents, such as asenapine, iloperidone and paliperidone cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence does not support that there is a general "class effect" in terms of either efficacy or harm for most off-label indications. Trials assessing the newer agents' efficacy and safety are necessary in each of the treatment areas if they are to be prescribed for off-label use.

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Abbreviations and Acronyms

ACES	Agitation-Calmness Evaluation Scale
ACTeRS	ADD-H Comprehensive Teachers Rating Scale
ADAS	Alzheimer's Disease Assessment Scale
ADDES-S	Attention-Deficit Disorders Evaluation Scale: Secondary-Age Student
ADHD	Attention-deficit hyperactivity disorder
ADHD-SC4	ADHD Symptom Checklist
AHRQ	Agency for Healthcare Research and Quality
ASEBA	Achenbach System for Empirically Based Assessment
ASI-drug	Addiction Severity Index Drug Composite Score
BAI	Beck Anxiety Inventory
BASC-2	Behavior Assessment System for Children-2
BDI	Beck Depression Inventory
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BMI	Body mass index
BPD	Borderline personality disorder
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelson Melancholia Scale
BSI	Brief Symptom Inventory
CAARS	Conners' Adult ADHD Rating Scales
CAPS	Clinician-Administered PTSD Scale
CAS-P	Children's Aggression Scale - Parent Version
CAS-T	Children's Aggression Scale - Teacher Version
CBT	Cognitive behavioral therapy
CCQ	Cocaine Craving Questionnaire
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative Effectiveness Review
CES-D	Center for Epidemiologic Studies Depression Scale
CGI-I	Clinical Global Impression Scale - Improvement subscale
CGI-S	Clinical Global Impression Scale - Severity Subscale
CI	Confidence interval
CIBIC	Clinician's Interview-Based Impression of Change
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMAI	Cohen-Mansfield Agitation Inventory
CSCAADD	Copeland Symptom Checklist for Adult Attention-Deficit Disorders
CVA	Cerebrovascular accident
DARE	Database of Abstracts of Reviews of Effects
DAS-A	Daily Assessment of Symptoms - Anxiety
DIS-Q	Dissociation Questionnaires
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
ED	Emergency department
EDEQ	Eating Disorders Examination Questionnaire Version
EMBASE	Biomedical and Pharmacological Bibliographic Database
EPC	Evidence-based Practice Center

EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
FGA	First generation antipsychotics
GAD	Generalized anxiety disorder
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D/HDRS	Hamilton Depression Rating Scale
ISQ	Insomnia Symptom Questionnaire
KQ	Key Question
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MMSE	Mini Mental Status Exam
MR	Mentally retarded
NC	Not calculated
NNH	Number needed to harm
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory, Nursing Home
OAS-M	Overt Aggression Scale-Modified
OCD	Obsessive-compulsive disorder
PANSS	Positive and Negative Symptom Scale
PCT	Placebo controlled trial
PD	Personality disorders
PDC	Depression Cluster
PRS	Parent's Rating Scale
PTSD	Post-traumatic stress disorder
QEWPR	Questionnaire on Eating and Weight Patterns- Revised
RCT	Randomized controlled trial
RR	Relative risks
SCHIP	State Children's Health Insurance Program
SCL-90	Symptom Checklist-90
SCL-90-R	Symptom Checklist-90-revised
SDS	Sheehan Disability Scale
SF36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIAB	Structured Interview for Anorexia and Bulimia
SNAP-IV	Swanson, Nolan and Pelham Rating Scale
SPI	Medical Outcomes Study (MOS) Sleep Problem Index
SRC	Scientific Resource Center
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAXI	State-Trait Anger Expression Inventory
TEP	Technical expert panel
TMR	Therapist Monitoring Record
TSSR	Tic Symptom Self Report
VA	U.S. Department of Veterans Affairs
WURS	Wender Utah Rating Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

ZAN-BPD

Zanarini Rating Scale for Borderline Personality Disorder

Appendix A. Literature Search Strategies



OFF-LABEL USE OF ATYPICAL ANTIPSYCHOTICS SEARCH METHODOLOGY

SEARCH #1 (Drug Utilization):

DATABASE & TIME PERIOD COVERED:

PubMed – 6/1/2008-9/9/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name]
AND
drug utilization OR pharmacoepidemiolog* OR utiliz*[tiab] OR utilis* OR use[ti] OR uses[ti]

NUMBER OF RESULTS: 34

SEARCH STRATEGY #2 (Drug Utilization):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/10/2009

paliperidone

AND

drug utilization OR pharmacoepidemiolog* OR utiliz*[tiab] OR utilis* OR use[ti] OR uses[ti]

NUMBER OF RESULTS: 10

SEARCH STRATEGY #3 (Drug Utilization):

DATABASE & DATES OF COVERAGE:

PsycINFO – 2008-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR paliperidone
AND

KW OR TI (drug utilization OR utiliz* OR utilis* OR use OR uses OR pharmacoepidemiolog*
)

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 366

SEARCH STRATEGY #4a (Anxiety)

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR

atypical antipsychotic* OR atypical anti-psychotic*

AND

("Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Anti-Anxiety Agents"[Mesh] OR "Anti-Anxiety Agents "[Pharmacological Action]) OR anxiety[tiab] OR anxious*[tiab] OR anti-anxiety[tiab] OR antianxiety[tiab]

NUMBER OF RESULTS: 1098

SEARCH STRATEGY #4b (Insomnia)

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR

atypical antipsychotic* OR atypical anti-psychotic*

AND

"Sleep Initiation and Maintenance Disorders"[Mesh] OR insomni*[tiab] OR sleep*[tiab]

NUMBER OF RESULTS: 370

SEARCH STRATEGY #4c (Autism):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR

atypical antipsychotic* OR atypical anti-psychotic*

AND

autism OR autistic

NUMBER OF RESULTS: 202

SEARCH STRATEGY #4d (ADHD):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR
atypical antipsychotic* OR atypical anti-psychotic*

AND

"Attention Deficit Disorder with Hyperactivity"[Mesh] OR attention deficit disorder[tiab] OR
adhd

NUMBER OF RESULTS: 158

SEARCH STRATEGY #4e (Anorexia/Bulimia):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR
atypical antipsychotic* OR atypical anti-psychotic*

AND

"Anorexia Nervosa"[Mesh] OR "Anorexia"[Mesh] OR ("Bulimia"[Mesh] OR "Bulimia
Nervosa"[Mesh]) OR anorexi*[tiab] OR bulimi*[tiab]

NUMBER OF RESULTS: 86

SEARCH STRATEGY #4f (Tourette Syndrome):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-9/24/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR
atypical antipsychotic* OR atypical anti-psychotic*

AND

"Tourette Syndrome"[Mesh] OR tourette*[tiab]

NUMBER OF RESULTS: 127

SEARCH STRATEGY #5:

DATABASE & DATES OF COVERAGE:

PubMed – 1966-10/13/2009

“Related Article” search on the following:

Leslie, D. L., S. Mohamed, et al. (2009) "Off-label use of antipsychotic medications in the department of Veterans Affairs health care system." Psychiatr Serv 60(9): 1175-81.

NUMBER OF RESULTS: 107

SEARCH STRATEGY #6 (Original Meds and Original Conditions):

DATABASE & DATES OF COVERAGE:

PubMed – 7/1/2008-10/13/2009

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR
"Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name]
OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name] OR atypical
antipsychotic* OR atypical anti-psychotic*

AND

"Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive Behavior"[Mesh] OR "Stress
Disorders, Post-Traumatic"[Mesh] OR "Personality Disorders"[Mesh] OR "Dementia"[Mesh]
OR "Depressive Disorder, Major"[Mesh] OR obsessive*[tiab] OR posttraumatic stress[tiab] OR
post-traumatic stress[tiab] OR post traumatic stress[tiab] OR ptsd[tiab] OR personality
disorder*[tiab] OR dementia[tiab] OR major depress*[tiab]

NUMBER OF RESULTS: 230

SEARCH STRATEGY #7 (Original Meds & Original Conditions):

DATABASE & DATES OF COVERAGE:

PsycINFO – 2008-11/13/2009

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole

AND

personality disorder* OR posttraumatic stress disorder OR post-traumatic stress OR ptsd or dementia OR "major depressive" OR obsessive-compulsive OR obsessive compulsive or dementia OR ((geriatric OR elderly) AND (agitation OR agitated))
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 165

SEARCH STRATEGY #8 (Original Meds & New Conditions):

DATABASE & DATES OF COVERAGE:

PsycINFO --1850-11/18/2009

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole

AND

anxiety OR anti-anxiety OR antianxiety OR insomnia OR sleep* OR anorexi* OR bulimi* OR tourett* OR attention deficit disorder OR adhd)

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 895

SEARCH STRATEGY #9 (New Meds):

DATABASE & DATES OF COVERAGE:

PubMed - 7/1/2008-10/13/2009

paliperidone

NOT

animal* NOT (human OR humans)

NUMBER OF RESULTS: 209

SEARCH STRATEGY #10 (New Meds):

DATABASE & DATES OF COVERAGE:

PubMed - 1966-11/13/2009

iloperidone OR asenapine

NUMBER OF RESULTS: 80

SEARCH STRATEGY #11 (New Meds):
DATABASE & DATES OF COVERAGE:
PsycINFO – 2008-11/18/2009

paliperidone OR iloperidone OR asenapine
Search modes - Phrase Searching (Boolean)
NUMBER OF RESULTS: 85

SEARCH STRATEGY #12 (Depression):
DATABASE & DATES OF COVERAGE:
PsycINFO – 2008-11/20/2009

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole
AND
depression OR depressive
AND
human
NOT
personality disorder* OR posttraumatic stress disorder OR post-traumatic stress OR ptsd or
dementia OR "major depressive" OR obsessive-compulsive OR obsessive compulsive or
dementia OR ((geriatric OR elderly) AND (agitation OR agitated))

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 137

SEARCH STRATEGY #13 (Substance Abuse):
DATABASE & DATES OF COVERAGE:
PsycINFO – ~1850-11/20/2009

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole
AND
substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR
cocaine OR heroin
AND
human

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 326

SEARCH STRATEGY #14 (Substance Abuse):

DATABASE & DATES OF COVERAGE:

PubMed – 1966-11/20/2009

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole

AND

substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR cocaine OR heroin OR "Substance-Related Disorders"[Mesh]

NOT

animal* NOT (human OR humans)

NUMBER OF RESULTS: 521

SEARCH STRATEGY #15 (Iloperidone & Asenapine):

DATABASE & DATES OF COVERAGE:

Embase – 1972-12/8/2009

iloperidone? or asenapine?

NUMBER OF RESULTS: 222

SEARCH ALERTS (Initiated 12/18/09)

PubMed

atypical antipsychotic* OR atypical anti-psychotic* OR olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole OR paliperidone OR iloperidone OR asenapine

PsycINFO

atypical antipsychotic* OR atypical anti-psychotic* OR olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole OR paliperidone OR asenapine OR iloperidone
Population Group: Human

Frequency: Monthly, Duration: Six months

Embase (updated 7/8/10 & alert set up)

'atypical antipsychotic'/exp OR 'atypical antipsychotic' OR 'atypical anti-psychotic' OR 'atypical anti psychotic' OR 'atypical anti-psychotics' OR 'atypical antipsychotics'/exp OR 'atypical antipsychotics' OR atypical AND antipsychotic AND agent OR 'olanzapine'/exp OR 'olanzapine' OR 'quetiapine'/exp OR 'quetiapine' OR 'risperidone'/exp OR 'risperidone' OR 'ziprasidone'/exp OR 'ziprasidone' OR 'aripiprazole'/exp OR 'aripiprazole' OR 'paliperidone'/exp OR 'paliperidone' OR 'iloperidone'/exp OR 'iloperidone' OR 'asenapine'/exp OR 'asenapine' AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim

OR [conference review]/lim OR [erratum]/lim OR [review]/lim OR [short survey]/lim) AND [humans]/lim AND [2010-2011]/py 988

SEARCH STRATEGY #16 (PubMed UPDATE – Drug Utilization):

DATABASE & DATES OF COVERAGE:

PubMed – 8/2009-1/2/2011

atypical antipsychotic* OR atypical anti-psychotic* OR olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole OR paliperidone OR iloperidone OR asenapine OR "Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name] OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name]

AND

drug utilization OR pharmacoepidemiolog* OR utiliz*[tiab] OR utilis* OR use[ti] OR uses[ti] OR off-label OR "off label" OR offlabel

NUMBER OF RESULTS: 101

SEARCH STRATEGY #17 (PubMed UPDATE - Insomnia):

DATABASE & DATES OF COVERAGE:

PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)

AND

("Sleep Initiation and Maintenance Disorders"[Mesh] OR insomni*[tiab] OR sleep*[tiab])

NUMBER OF RESULTS: 75

SEARCH STRATEGY #18 (PubMed UPDATE - Autism):

DATABASE & DATES OF COVERAGE:

PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)

AND

autism OR autistic

NUMBER OF RESULTS: 43

SEARCH STRATEGY #19 (PubMed UPDATE - ADHD):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR
aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
"Attention Deficit Disorder with Hyperactivity"[Mesh] OR attention deficit disorder[tiab] OR
adhd

NUMBER OF RESULTS: 38

SEARCH STRATEGY #20 (PubMed UPDATE – Eating Disorders):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR
aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
"Anorexia Nervosa"[Mesh] OR "Anorexia"[Mesh] OR ("Bulimia"[Mesh] OR "Bulimia
Nervosa"[Mesh]) OR anorexi*[tiab] OR bulimi*[tiab]

NUMBER OF RESULTS: 12

SEARCH STRATEGY #21 (PubMed UPDATE – Tourette Syndrome):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR
aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
"Tourette Syndrome"[Mesh] OR tourette*[tiab]

NUMBER OF RESULTS: 16

SEARCH STRATEGY #22 (PubMed UPDATE – Substance Abuse):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR cocaine OR heroin OR "Substance-Related Disorders"[Mesh]

NUMBER OF RESULTS: 173

SEARCH STRATEGY #23 (PubMed UPDATE – Personality Disorders):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
"Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive Behavior"[Mesh] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "Personality Disorders"[Mesh] OR "Dementia"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR obsessive*[tiab] OR posttraumatic stress[tiab] OR post-traumatic stress[tiab] OR post traumatic stress[tiab] OR ptsd[tiab] OR personality disorder*[tiab] OR dementia[tiab] OR major depress*[tiab]

NUMBER OF RESULTS: 225

SEARCH STRATEGY #24 (PubMed UPDATE – Anxiety):
DATABASE & DATES OF COVERAGE:
PubMed – 8/2009-1/2/2011

"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone)
AND
"Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Anti-Anxiety Agents"[Mesh] OR "Anti-Anxiety Agents "[Pharmacological Action]) OR anxiety[tiab] OR anxious*[tiab] OR anti-anxiety[tiab] OR antianxiety[tiab]

NUMBER OF RESULTS: 155

SEARCH STRATEGY #25 (PsycINFO UPDATE – Drug Utilization):
DATABASE & DATES OF COVERAGE:
PsycINFO – 8/2009-1/6/2011

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR paliperidone
AND
drug utilization OR utiliz* OR utilis* OR use OR uses OR Pharmacoepidemiolog*
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 189

SEARCH STRATEGY #26 (PsycINFO UPDATE – Off-Label):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR paliperidone
AND
off-label OR "off label" OR offlabel
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 4

SEARCH STRATEGY #27 (PsycINFO UPDATE – Personality Disorders):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR paliperidone
AND
personality disorder* OR posttraumatic stress disorder OR post-traumatic stress OR ptsd or
dementia OR "major depressive" OR obsessive-compulsive OR obsessive compulsive or
dementia OR ((geriatric OR elderly) AND (agitation OR agitated))
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 111

SEARCH STRATEGY #28 (PsycINFO UPDATE – Other Disorders):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR paliperidone
AND
anxiety OR anti-anxiety OR antianxiety OR insomnia OR sleep* OR anorexi* OR bulimi* OR
tourett* OR attention deficit disorder OR adhd
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 137

SEARCH STRATEGY #29 (PsycINFO UPDATE – Three specific drugs):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

iloperidone OR asenapine OR paliperidone
Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 60

SEARCH STRATEGY #30 (PsycINFO UPDATE – Depression):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole
AND

depression OR depressive

NOT

personality disorder* OR posttraumatic stress disorder OR post-traumatic stress OR ptsd or
dementia OR "major depressive" OR obsessive-compulsive OR obsessive compulsive or
dementia OR ((geriatric OR elderly) AND (agitation OR agitated))

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 95

SEARCH STRATEGY #31 (PsycINFO UPDATE – Substance Abuse):

DATABASE & DATES OF COVERAGE:

PsycINFO – 8/2009-1/6/2011

olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole
AND

substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR
cocaine OR heroin

Search modes - Phrase Searching (Boolean)

Population Group: Human

NUMBER OF RESULTS: 47

SEARCH STRATEGY #32 (PsycINFO UPDATE – General Atypical Antipsychotics):
DATABASE & DATES OF COVERAGE:
PsycINFO – 8/2009-1/6/2011

atypical antipsychotic* OR atypical anti-psychotic*
Population Group: Human

Search modes - Phrase Searching (Boolean)

NUMBER OF RESULTS: 326

SEARCH STRATEGY #33 (Embase UPDATE – Systematic Reviews, Meta-Analyses, Clinical Trials):

DATABASE & DATES OF COVERAGE:
Embase – 1999-5/12/2011

SEARCH STRATEGY:

'olanzapine'/exp OR 'quetiapine'/exp OR 'risperidone'/exp OR 'ziprasidone'/exp OR
'aripiprazole'/exp OR 'iloperidone'/exp OR 'asenapine'/exp OR 'paliperidone'/exp OR 'atypical
antipsychotic'/exp OR 'atypical antipsychotics'/exp OR 'atypical anti-psychotic' OR 'atypical anti-
psychotics' OR 'atypical antipsychotic agent'/exp

AND

utilization OR utiliz* OR utilis* OR use OR uses OR pharmacoepidemiolog* OR 'off-label' OR
'off label' OR offlabel OR 'personality disorder'/exp OR 'personality disorders'/exp OR 'post-
traumatic stress'/exp OR 'posttraumatic stress disorder'/exp OR 'ptsd'/exp OR 'dementia'/exp OR
'major depressive' OR 'major depression'/exp OR 'obsessive compulsive' OR 'obsessive-
compulsive disorder'/exp OR (geriatric OR 'elderly'/exp) AND ('agitation'/exp OR agitated) OR
'anxiety'/exp OR 'anti-anxiety' OR antianxiety OR insomnia* OR sleep* OR anorexi* OR
bulimi* OR tourett* OR 'attention deficit disorder'/exp OR 'adhd'/exp OR 'depression'/exp OR
depressive OR 'alcohol abuse'/exp OR 'alcoholism'/exp OR 'substance abuse'/exp OR addict* OR
'cocaine'/exp OR 'heroin'/exp OR autism'/exp OR autistic

AND

[cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized
controlled trial]/lim OR [systematic review]/lim)

NUMBER OF RESULTS: 684

SEARCH STRATEGY #34 (Embase UPDATE – Observational Studies)

DATABASE & DATES OF COVERAGE:
Embase – 1999-5/12/2011

SEARCH STRATEGY:

'olanzapine'/exp OR 'quetiapine'/exp OR 'risperidone'/exp OR 'ziprasidone'/exp OR
'aripiprazole'/exp OR 'iloperidone'/exp OR 'asenapine'/exp OR 'paliperidone'/exp OR 'atypical
antipsychotic'/exp OR 'atypical antipsychotics'/exp OR 'atypical anti-psychotic' OR 'atypical anti-
psychotics' OR 'atypical antipsychotic agent'/exp

AND

utilization OR utiliz* OR utilis* OR use OR uses OR pharmacoepidemiolog* OR 'off-label' OR
'off label' OR offlabel OR 'personality disorder'/exp OR 'personality disorders'/exp OR 'post-
traumatic stress'/exp OR 'posttraumatic stress disorder'/exp OR 'ptsd'/exp OR 'dementia'/exp OR
'major depressive' OR 'major depression'/exp OR 'obsessive compulsive' OR 'obsessive-
compulsive disorder'/exp OR (geriatric OR 'elderly'/exp) AND ('agitation'/exp OR agitated) OR
'anxiety'/exp OR 'anti-anxiety' OR antianxiety OR insomnia* OR sleep* OR anorexi* OR
bulimi* OR tourett* OR 'attention deficit disorder'/exp OR 'adhd'/exp OR 'depression'/exp OR
depressive OR 'alcohol abuse'/exp OR 'alcoholism'/exp OR 'substance abuse'/exp OR addict* OR
'cocaine'/exp OR 'heroin'/exp OR autism'/exp OR autistic

AND

observational

AND

[humans]/lim

NUMBER OF RESULTS: 111

Appendix B. Data Collection Forms

Short Form Screener

SCEPC Atypical Anti-Psychotic Drug Review Update
Article Screener
FINAL 12/11/2009

Article ID:

Citation:

1. Research topic(s): Check all that apply

- Aripiprazole
- Asenapine
- Iloperidone
- Olanzapine
- Quetiapine
- Paliperidone
- Risperidone
- Ziprasidone
- Entire class
- None of the above (STOP)

2. Condition(s) studied: Check all that apply

- Anxiety
- Dementia/severe geriatric agitation....
- Depression
- Insomnia
- Obsessive-compulsive disorder
- Personality disorders (DSM IV).....
- PTSD
- Substance abuse
- Eating disorder (incl children 17 & under) ..
- ADHD (incl children 17 & under).....
- Tourette's (incl children 17 & under)
- None of the above (STOP)

3. Study population: Circle one

- Human included 1
- Only animal or cell lines 2 (STOP)

4. Study design: Circle one

- Descriptive (historical, editorial etc.) 1 (STOP)
- Non-systematic review 2 (STOP)
- Systematic review / meta-analysis 3 (STOP)
- Case report 4 (STOP)
- Case series 5
- Cohort 6
- Case control 7
- RCT *only* 8
- CCT *only* 9
- Trial + Open label extension 10
- Other design 11

5. Was a placebo used in this study? Circle one

- Yes 1
- No 2

6. Total sample size entering study. If not reported then total completing sample size:

Enter # or 999 if no sample reported

7. Does article report on the following: Check all that apply

- Efficacy
- Safety / Adverse events
- Utilization / Prescribing patterns
- None of the above (STOP)

**8. Total duration of study:
For Duration enter # or 999 if not reported.
For Units enter code from below.**

<div style="border: 1px solid black; width: 100%; height: 20px;"></div> <p>Duration</p>	<div style="border: 1px solid black; width: 100%; height: 20px;"></div> <p>Units</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td>01. Hour</td> <td>03. Week</td> <td>05. Year</td> </tr> <tr> <td>02. Day</td> <td>04. Month</td> <td>99. NR</td> </tr> </table>	01. Hour	03. Week	05. Year	02. Day	04. Month	99. NR
01. Hour	03. Week	05. Year					
02. Day	04. Month	99. NR					

9. Language of article: Circle one

- English 1
- Other 2
- Specify : _____

10. Do you think that this article might be a duplicate or include the same data as another study? Circle one

- No 1
- Yes 2
- If YES, ID#: _____

11. Do you think that this article might be part of a large or named trial? Circle one

- No 1
- Yes 2
- If YES, trial name: _____

12. Is there a reference that needs to be ordered? Circle one

- No 1
- Yes 2
- If YES, Ref #: _____

NOTES:

Detailed Abstraction Form

**RAND SCEPC Anti-Psychotic Drugs Update Project
Detailed Abstraction Form**

FINAL 05-21-2010

Article ID: _____	Reviewer: _____
First Author: _____	(Last Name Only)
Study Number: _____ of _____	Description: _____
(Enter '1' if only one)	(if more than one study)

1. Related Studies Flag: (ENTER 99 FOR NONE)
ID numbers of articles that contributed data to this form:
_____, _____, _____, _____, _____
2. Is the study design trial with crossover? (CIRCLE ONE)
Yes 1
No 2
3. Was the study described as randomized? (CIRCLE ONE)
Yes 1
No 2
4. Treatment Allocation
 - a. Was the method of randomization adequate? (CIRCLE ONE)
Yes 1
No 2
Don't know 9
 - b. Was the treatment allocation concealed? (CIRCLE ONE)
Yes 1
No 2
Don't know 9
5. Were groups similar at baseline regarding the most important prognostic indicators? (CIRCLE ONE)
Yes 1
No 2
Don't know 9

6. Is the study described as: (CIRCLE ONE)
Double blind 1
Single blind, patient 2
Single blind, outcome assessment 3
Single blind, not described 4
Open 5
Blinding not described 8
Not applicable 9
7. If reported, was the method of double blinding appropriate? (CIRCLE ONE)
Yes 1
No 2
Double blinding method not described 8
Not applicable 9
8. Was the outcome assessor blinded? (CIRCLE ONE)
Yes 1
No 2
Don't know 9
9. Was the care provider blinded? (CIRCLE ONE)
Yes 1
No 2
Don't know 9
10. Were patients blinded? (CIRCLE ONE)
Yes 1
No 2
Don't know 9
11. Drop-out rate questions: (CIRCLE ONE)
 - a. Was the drop-out rate described and the reason given?
Yes 1
No 2
Don't know 9
 - b. Was the drop-out rate acceptable? (CIRCLE ONE)
Yes 1
No 2
Don't know 9

**RAND SCEPC Anti-Psychotic Drugs Update Project
Detailed Abstraction Form**

12. Were all randomized participants analyzed in the group to which they were originally assigned? (CIRCLE ONE)

- Yes..... 1
- No..... 2
- Don't know..... 9

13. Other sources of potential bias: (CIRCLE ONE)

a. Were co-interventions avoided or similar?

- Yes..... 1
- No..... 2
- Don't know..... 9

b. Was the compliance acceptable in all groups? (CIRCLE ONE)

- Yes..... 1
- No..... 2
- Don't know..... 9

c. Was the outcome assessment timing similar in all groups? (CIRCLE ONE)

- Yes..... 1
- No..... 2
- Don't know..... 9

14. What is the study trial name?

Enter code or 999 for no name: _____

15. What was the study's setting? (CHECK ALL THAT APPLY)

- Multi-center.....
- Single setting.....
- Community practice.....
- Long-term care facilities.....
- VA Healthcare System.....

Other (enter code: _____),

Setting not reported.....

16. What was the study's funding source? (CHECK ALL THAT APPLY)

Government.....

Hospital.....

Industry.....

Private (non-industry).....

Other (enter code: _____).....

Unclear.....

Not reported.....

17. Did the article include a statement on the role of the funder? (CIRCLE ONE)

Yes..... 1

No..... 2

18. In what area was the study conducted? (CHECK ALL THAT APPLY)

US.....

Canada.....

UK.....

Western Europe.....

Eastern Europe.....

Australia/New Zealand.....

Asia.....

Middle East.....

Latin America.....

Other Country (spec: _____).....

Not reported.....

19. What was the percent of male participants?

(ENTER NUMBER OR 999)

___ %

20. What was the racial/ethnic population studied? (Check all that apply)

Caucasian.....

African Ancestry.....

Hispanic.....

Asian/Pacific Islander.....

Native American.....

Eskimo/Inuit.....

Mixed.....

Other-Not otherwise specified.....

Not reported.....

**RAND SCEPC Anti-Psychotic Drugs Update Project
Detailed Abstraction Form**

21. What were reported for the following questions regarding subjects' ages? (Enter number 999 for not reported)

Mean Age _____

Median Age _____

Age Range _____ to _____

22. What were the study's inclusion criteria?

Text: _____

23. What were the study's exclusion criteria?

Text: _____

24. What were the comorbidities reported in the study?

(Check All That Apply)

Anxiety

Dementia/severe geriatric agitation..

Depression.....

Insomnia.....

Obsessive-compulsive disorder

Personality disorders (DSM IV).....

PTSD.....

Substance abuse.....

Eating disorder (incl children 17 & under) ..

ADHD (incl children 17 & under)

Tourette's (incl children 17 & under)

Enter codes for others: _____, _____, _____,

_____, _____, _____, _____, _____,

_____, _____, _____, _____, _____,

25. Run-in period table: (Enter 998 if not described; enter 999 if no run-in.)

Length	Units	Placebo/Medication	How used for randomization?

26. Wash-out period table:

(Enter 998 if not described; enter 999 if no wash-out.)

Length	Units	Placebo/Medication	How used for randomization?

27. Time of assessment: When were outcomes measured?

(Enter the number/code in the appropriate box, or circle YES/NO.)

Baseline?	YES / NO	
Follow-up	Number	Unit
1 st		
2 nd		
3 rd		
4 th		
5 th		
6 th		
7 th		
8 th		
Additional		

Units for Q25, Q26, Q27
1. Hour
2. Day
3. Week
4. Biweekly
5. Month
6. Year
7. Not described
8. Not Applicable
9. Not Reported
10. Min
11. Weekly
12. Monthly

**RAND SCEPC Anti-Psychotic Drugs Update Project
Detailed Abstraction Form**

INTERVENTIONS

33. Enter sample size and intervention data for each arm beginning with placebo or control, then in order of first mention.

Arm/ Group	Sample size	Intervention	Dose	Units	Frequency	Dose Description	Duration of treatment	Units	Co-Intervention(s)
1	_____ N ENTERING	Placebo..... <input type="checkbox"/> Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	_____ N COMPLETING	Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/> Code: _____							
2	_____ N ENTERING	Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	_____ N COMPLETING	Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/> Code: _____							
3	_____ N ENTERING	Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	_____ N COMPLETING	Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/> Code: _____							
	Enter a number for N entering and N completing or enter 999 if not reported.	Check box for intervention or enter code(s) from list. Put placebo in first arm.	Enter # or range 998 Not Applicable 999 Not Reported	Enter a number 1. g 2. mg 3. tablets 9. Not Reported	Enter a number 1. Hour 2. Day 3. Week 4. Biweekly 5. Month 6. Year 9. NR	Enter a number 1. Fixed single dose 2. Fixed titration schedule 3. Flexible dose 4. Average final dose 9. Not Reported	Enter a number 997. Variable 998. Not Applicable 999. Not Reported	Enter a number 1. Hour 2. Day 3. Week 4. Biweekly 5. Month 6. Year 8. Not Applic. 9. NR	Enter code(s) or 998. Not Applicable 999. Not Reported

**RAND SCEPC Anti-Psychotic Drugs Update Project
Detailed Abstraction Form**

Interventions (continued)

Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.

Arm/ Group	Sample size	Intervention	Dose	Units	Frequency	Dose Description	Duration of treatment	Units	Co-intervention(s)
4	N ENTERING	Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/> Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	N COMPLETING	Code: _____							
5	N ENTERING	Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/> Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	N COMPLETING	Code: _____							
6	N ENTERING	Aripiprazole..... <input type="checkbox"/> Asenapine..... <input type="checkbox"/> Iloperidone..... <input type="checkbox"/> Olanzapine..... <input type="checkbox"/> Quetiapine..... <input type="checkbox"/> Paliperidone..... <input type="checkbox"/> Risperidone..... <input type="checkbox"/> Ziprasidone..... <input type="checkbox"/>	_____	_____	_____	_____	_____	_____	_____ _____ _____
	N COMPLETING	Code: _____							
	Enter a number for N entering and N completing or enter 999 if not reported	Check box for intervention or enter code(s) from list. Put placebo in first arm.	Enter # or range 998. Not Applicable 999. Not Reported	Enter a number 1. g 2. mg 3. tablets 9. Not Reported	Enter a number 1. Hour 2. Day 3. Week 4. Biweekly 5. Month 6. Year 9. NR	Enter a number 1. Fixed single dose 2. Fixed titration schedule 3. Flexible dose 4. Average final dose 9. Not Reported	Enter a number 997. Variable 998. Not Applicable 999. Not Reported	Enter a number 1. Hour 2. Day 3. Week 4. Biweekly 5. Month 6. Year 8. Not Applicable 9. NR	Enter code(s) or 998. Not Applicable 999. Not Reported

Note: If there are more than six arms to the study, please print another page for adding arms 7, 8, 9, etc.

Appendix C. Previously Published Meta-Analyses

Depression

Aripiprazole Efficacy

RCTs (Author, year)	Meta-analysis (Aripiprazole)	
	Arbaizar, 2009 ³⁰¹	Nelson, 2009 ¹⁵²
Berman, 2007 ¹⁵⁵	X	X
Marcus, 2008 ¹⁵⁴	X	X
Berman, 2008: same study as ¹⁵⁶		X

Olanzapine Efficacy

RCTs (Author, year)	Meta-analysis (Olanzapine)	
	Nelson, 2009 ¹⁵²	Papakostas, 2007 ¹⁵¹
Shelton, 2001 ³⁰²	X	X
Shelton, 2005 ³⁰³	X	X
Corya, 2006 ³⁰⁴	X	X
Thase, 2007 ¹⁷⁴	X	
Thase, 2006 same study as ¹⁷⁴		X

Risperidone Efficacy

RCTs (Author, year)	Meta-analysis (Risperidone)	
	Nelson, 2009 ¹⁵²	Papakostas, 2007 ¹⁵¹
Mahmoud, 2007 ¹⁶⁶	X	
Reeves, 2008 ¹⁶⁴	X	
Keitner, 2009 ¹⁶⁵	X	
Keitner, 2006 not included		X
Gharabawi, 2006 same study as ¹⁶⁷		X

Quetiapine Efficacy

RCTs (Author, year)	Meta-analysis (Quetiapine)	
	Nelson, 2009 ¹⁵²	Papakostas, 2007 ¹⁵¹
Mattingly, 2006 ¹⁶¹	X	X
McIntyre, 2007 ⁸⁶	X	
El-Khalili, 2008 ³⁰⁵	X	
Khullar, 2006 not included	X	X
Earley, 2007 same study as ³⁰⁶	X	
McIntyre, 2006 same study as ⁸⁶		X

PTSD

Risperidone Efficacy

RCTs (Author, year)	Meta-analysis (Risperidone)
	Pae, 2008 ²²⁸
Bartzokis, 2005 ²³⁰	X
Reich, 2004 ²³¹	X
Monnelly, 2003 ²³²	X
Padala, 2006 ²³³	X
Hamner, 2003 ²³⁴	X

Olanzapine Efficacy

RCTs (Author, year)	Meta-analysis (Olanzapine)
	Pae, 2008 ²²⁸
Stein, 2002 ²³⁵	X
Butterfield, 2001 ²³⁶	X

Risperidone AE

RCTs (Author, year)	Meta-analysis (Risperidone)
	Pae, 2008 ²²⁸
Bartzokis, 2005 ²³⁰	X
Reich, 2004 ²³¹	X
Monnelly, 2003 ²³²	X
Padala, 2006 ²³³	X
Hamner, 2003 ²³⁴	X

Olanzapine AE

RCTs (Author, year)	Meta-analysis (Olanzapine)
	Pae, 2008 ²²⁸
Stein, 2002 ²³⁵	X
Butterfield, 2001 ²³⁶	X

Personality Disorder

Olanzapine Efficacy

RCTs (Author, year)	Meta-analysis (Olanzapine)
	Ingenhoven, 2010 ²¹³
Zanarini, 2001 ²¹⁴	X
Soler, 2005 ²¹⁵	X
Bogenschutz, 2004 ²¹⁶	X

Risperidone Efficacy

RCTs (Author, year)	Meta-analysis (Risperidone)
	Ingenhoven, 2010 ²¹³
Koenigsberg, 2003 ²¹⁷	X

Aripiprazole Efficacy

RCTs (Author, year)	Meta-analysis (Aripiprazole)
	Ingenhoven, 2010 ²¹³
Nickel, 2006 ²¹⁸	X

Substance Abuse

Risperidone Efficacy

RCTs (Author, year)	Meta-analysis (Aripiprazole)
	Amato, 2007 ²⁷⁵
Grabowski, 2004 ²⁷⁴	X
Levin, 1999 ²⁶⁸	X
Smelson, 2004 ²⁷⁰	X

Olanzapine Efficacy

RCTs (Author, year)	Meta-analysis (Aripiprazole)
	Amato, 2007 ²⁷⁵
Kampman, 2003 ²⁶⁴	X
Reid, 2005 ²⁶⁵	X
Smelson, 2006 ²⁴⁵	X

Anxiety

Quetiapine Efficacy

RCTs (Author, year)	Meta-analysis (Quetiapine)
	Depping, 2010 ⁸²
Bundelow, 2007 ⁸⁸	X
Eriksson, 2008	X
Joyce, 2008 ⁹⁴	X
Merideth, 2008 ⁸⁷	X

Appendix D. Evidence Tables

Head-to-Head Trials

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Rainer et al. 2007¹⁴²</p> <p>Dementia/Agitation</p> <p>Quetiapine, Risperidone</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 55</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 72</p> <p>Entering: 72</p> <p>Withdrawn: 6</p> <p>Lost to follow-up: 1</p> <p>Analyzed: 65</p> <p>Method of AE assessment: Elicited</p>	<p>Inclusion criteria: 55-85 years old, dementia, MMSE score 10-26, have a NPI part I score in sub-items relating to delusions, hallucinations, agitation/aggression</p> <p>Exclusion criteria: Participation in any other drug trial within 4 weeks, hypersensitive to study drugs, chronic disease, use of antipsychotics, seizure, severe cardiovascular disease, asthmatic condition, met NINCDS-ADRDA exclusion criteria.</p> <p>Interventions: Quetiapine 50-400 mg/days flexible dose for 8 weeks vs Risperidone 0.5-4 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 28, 56 days</p>	<p>Results: Dementia: Change in CMAI (Agitation) at 8 weeks: Risperidone vs Quetiapine - SMD = -0.17 (-0.66 , 0.32)</p> <p>Dementia: Change in NPI total (Total) at 8 weeks: Risperidone vs Quetiapine - SMD = -0.06 (-0.55 , 0.43)</p> <p>Adverse Events: Quetiapine vs Risperidone All Adverse Events: 57.9%(22/38) vs 44.1%(15/34) Asthenia: 2.6%(1/38) vs 5.9%(2/34) Cerebrovascular Adverse Events: 0.0%(0/38) vs 0.0%(0/34) Conjunctivitis: 0.0%(0/38) vs 5.9%(2/34) Constipation: 5.3%(2/38) vs 2.9%(1/34) Deaths: 0.0%(0/38) vs 0.0%(0/34) Diarrhea: 0.0%(0/38) vs 14.7%(5/34) Fall With Contusion: 2.6%(1/38) vs 0.0%(0/34) Falls Or Fractures Due To Somnolence Or Sedation: 0.0%(0/38) vs 0.0%(0/34) Fatigue: 7.9%(3/38) vs 0.0%(0/34) Femur Fracture: 5.3%(2/38) vs 0.0%(0/34) Insomnia: 5.3%(2/38) vs 2.9%(1/34) Muscle Rigidity: 0.0%(0/38) vs 14.7%(5/34) Sedation: 10.5%(4/38) vs 0.0%(0/34) Serious Adverse Events Of Hallucinations During Hospitalization For Hernia Surgery: 0.0%(0/38) vs 2.9%(1/34) Significant Change From Baseline Blood Pressure Or Pulse Rate: 0.0%(0/38) vs 0.0%(0/34) Somnolence: 5.3%(2/38) vs 0.0%(0/34) Thigh Fracture: 5.3%(2/38) vs 0.0%(0/34) Total Serious Adverse Events: 7.9%(3/38) vs 2.9%(1/34) Treatment-Emergent Extrapyramidal Symptoms Reported As Adverse Events (Extrapyramidal Disorder And Muscle Rigidity): 0.0%(0/38) vs 17.6%(6/34) Urinary Incontinence: 5.3%(2/38) vs 0.0%(0/34)</p> <p>Withdrawals:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
by investigator, reported spontaneously by patient		Quetiapine vs Risperidone Withdrawals:10.5%(4/38) vs 8.8%(3/34) Withdrawals Due To Adverse Events:5.3%(2/38) vs 2.9%(1/34)
<p>Sultzer et al. 2008¹¹⁹</p> <p>Dementia/Agitation</p> <p>Olanzapine, Quetiapine, Risperidone</p> <p>Location: US</p> <p>Trial: CATIE-AD</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 1</p> <p>Age: Mean: 78</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 421</p> <p>Withdrawn: 77-85%</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Not applicable</p>	<p>Inclusion criteria: Had dementia of the Alzheimer's type or probable Alzheimer's disease, delusions/hallucinations/agitation/ aggression, had occurred nearly every day over previous week or intermittently over 4 weeks, at least moderate in severity on BPRS, MMSE score 5-16</p> <p>Exclusion criteria: Patients in skilled nursing homes, taking antidepressants or anticonvulsants for mood stabilization.</p> <p>Interventions: Placebo for 12 weeks vs Olanzapine 5.5 mg/days average final dose for 12 weeks vs Quetiapine 56.5 mg/days average final dose for 12 weeks vs Risperidone 1.0 mg/days average final dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 56, 84 days</p>	<p>Results: Dementia: Change in NPI total (Total) at 12 weeks: Placebo vs Olanzapine - SMD = 0.15 (-0.11 , 0.40)</p> <p>Dementia: Change in NPI total (Total) at 12 weeks: Placebo vs Risperidone - SMD = 0.40 (0.13 , 0.68)</p> <p>Dementia: Change in NPI total (Total) at 12 weeks: Placebo vs Quetiapine - SMD = 0.15 (-0.11 , 0.42)</p> <p>Dementia: Change in NPI total (Total) at 12 weeks: Olanzapine vs Quetiapine - SMD = 0.02 (-0.27 , 0.30)</p> <p>Dementia: Change in NPI total (Total) at 12 weeks: Risperidone vs Quetiapine - SMD = -0.24 (-0.53 , 0.06)</p> <p>Dementia: Change in NPI total (Total) at 12 weeks: Risperidone vs Olanzapine - SMD = -0.27 (-0.56 , 0.02)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Placebo vs Olanzapine - SMD = 0.07 (-0.19 , 0.33)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Placebo vs Risperidone - SMD = 0.39 (0.11 , 0.66)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Placebo vs Quetiapine - SMD = 0.16 (-0.10 , 0.42)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Olanzapine vs Quetiapine - SMD = 0.07 (-0.21 , 0.35)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Risperidone vs Quetiapine - SMD = -0.24 (-0.54 , 0.06)</p> <p>Dementia: Change in BPRS psy (Psychosis) at 12 weeks: Risperidone vs Olanzapine - SMD = -0.27 (-0.56 , 0.02)</p> <p>Dementia: Change in BPRS agitation (Agitation) at 12 weeks:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
		<p>Placebo vs Olanzapine - SMD = 0.28 (0.02 , 0.54)</p> <p>Dementia: Change in BPRS agitation (Agitation) at 12 weeks: Placebo vs Risperidone - SMD = 0.10 (-0.18 , 0.37)</p> <p>Dementia: Change in BPRS agitation (Agitation) at 12 weeks: Placebo vs Quetiapine - SMD = 0.20 (-0.06 , 0.46)</p> <p>Dementia: Change in BPRS agitation (Agitation) at 12 weeks: Olanzapine vs Quetiapine - SMD = -0.09 (-0.37 , 0.19)</p> <p>Dementia: Change in BPRS agitation (Agitation) at 12 weeks: Risperidone vs Quetiapine - SMD = 0.10 (-0.20 , 0.39)</p>
<p>Maina et al. 2008¹⁹⁵</p> <p>OCD</p> <p>Olanzapine, Risperidone</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not funded</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Mean: 35</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 110</p>	<p>Inclusion criteria: Age >=18, primary diagnosis of OCD, OCD present for at least 1 year prior to study entry, VBOCS total score >=16, non-responders to SRIs</p> <p>Exclusion criteria: A current diagnosis of MDD and/or HAM-D score >=15, schizophrenia or organic brain syndrome or medical illness contra-indicate use of SRI and/or risperidone or olanzapine, pregnant or nursing women</p> <p>Interventions: Risperidone 1-3 mg/days fixed titration schedule for 8 weeks vs Olanzapine 2.5-10 mg/days fixed titration schedule for 8 weeks</p> <p>Run-in/wash-out period: Run-in: SRI monotherapy for 16 week(s). Patients resistant to SRI were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 42,</p>	<p>Results: OCD: Change in YBOCS (Total Score) at 8 weeks: Olanzapine vs Risperidone - WMD = -0.50 (-3.81 , 2.81)</p> <p>Adverse Events: Risperidone vs Olanzapine Amenorrhoea: 24.0%(6/25) vs 4.0%(1/25) Any Adverse Events: 52.0%(13/25) vs 64.0%(16/25) Diminished Sexual Desire: 0.0%(0/25) vs 4.0%(1/25) Micturition Disturbances: 4.0%(1/25) vs 0.0%(0/25) Nausea/Vomiting: 8.0%(2/25) vs 0.0%(0/25) Orthostatic Dizziness: 12.0%(3/25) vs 8.0%(2/25) Rash: 4.0%(1/25) vs 0.0%(0/25) Rigidity: 8.0%(2/25) vs 0.0%(0/25) Tension/Inner Unrest: 24.0%(6/25) vs 0.0%(0/25) Weight Gain: 16.0%(4/25) vs 52.0%(13/25)</p> <p>Withdrawals: Olanzapine Diminished Sex Desire; Weight Gain Leading To Withdrawal:8.0%(2/25) Risperidone Tension/Inner Unrest; Nausea/Vomiting Leading To Withdrawal:8.0%(2/25) Risperidone vs Olanzapine Withdrawals:12.0%(3/25) vs 16.0%(4/25) Withdrawals Due To Adverse Events:8.0%(2/25) vs 8.0%(2/25)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Eligible: 50 Entering: 50 Withdrawn: 7 Lost to follow-up: 0 Analyzed: 43</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>56 days</p>	
<p>Matsunaga et al. 2009¹⁹⁸</p> <p>OCD</p> <p>Olanzapine, Quetiapine, Risperidone</p> <p>Location: Asia</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 1</p> <p>Age: Mean: 30</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 137 Eligible: 44 Entering: 90</p>	<p>Inclusion criteria: Diagnosed OCD, received treatment \geq 1 year at Osaka hospital.</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Olanzapine 1-10 mg/days frequency not reported for duration not reported vs Quetiapine 25-100 mg/days frequency not reported for variable duration vs Risperidone 1-5 mg/days frequency not reported for duration not reported vs Control Group</p> <p>Run-in/wash-out period: Run-in: Fluoxetine or paroxetine for 12 week(s). Non-responders were randomized.</p> <p>Comorbidities: Depression</p> <p>Timing of outcome assessment: 365 days</p>	<p>Results: OCD: Insufficient data to calculate an effect size</p> <p>Adverse Events: SSRI+olanzapine, quetiapine or risperidone Increased Appetite: 34.1%(15/44) Increased Body Weight: 27.3%(12/44) Sedation: 6.8%(3/44) Sleepiness: 11.4%(5/44) SSRI+olanzapine, quetiapine or risperidone vs SSRIs (fluvoxamine or paroxetine) BMI Increase > 10%: 50.0%(22/44) vs 15.2%(7/46)</p> <p>Withdrawals: SSRI+olanzapine, quetiapine or risperidone Withdrawals:0.0%(0/44) SSRI+olanzapine, quetiapine or risperidone vs SSRIs (fluvoxamine or paroxetine) Withdrawals Due To Adverse Events:0.0%(0/44) vs 0.0%(0/46)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Withdrawn: NR Lost to follow-up: NR Analyzed: 46</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>		
<p>Nejtek et al. 2008²⁵⁰</p> <p>Substance abuse</p> <p>Quetiapine, Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry, Private</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 4</p> <p>Age: Mean: 36</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: 651 Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR</p>	<p>Inclusion criteria: 20-50 years old, outpatients, bipolar disorder with or without psychotic features or bipolar II disorder, cocaine or methamphetamine dependence, experiencing hypomanic, manic, or mixed state episodes with YMRS \geq9, craving score $>$-10 on SCQ - 10</p> <p>Exclusion criteria: Inpatients, substance-induced mood disorder, pregnant, a history of special education / mental retardation / dementia, had HIV/AIDS, reactive hepatitis, hepatic cirrhosis or any active liver disease, diabetes, heart disease, central nervous system disease, allergic to study medications, receiving any antipsychotic drugs, had contraindications</p> <p>Interventions: Quetiapine 50-600 mg/days fixed titration schedule for 20 weeks vs Risperidone 0.5-6 mg/days fixed titration schedule for 20 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: OCD, PTSD</p> <p>Timing of outcome assessment: 7, 14, 21,</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Adverse Events: Quetiapine vs Risperidone Blurred Vision: 2.1%(1/48) vs 6.5%(3/46) Clumsiness: 4.2%(2/48) vs 4.3%(2/46) Constipation: 2.1%(1/48) vs 0.0%(0/46) Daytime Sleepiness: 12.5%(6/48) vs 10.9%(5/46) Decreased Appetite: 6.3%(3/48) vs 6.5%(3/46) Diarrhea: 2.1%(1/48) vs 2.2%(1/46) Difficulty Urinating: 0.0%(0/48) vs 0.0%(0/46) Dizziness: 4.2%(2/48) vs 2.2%(1/46) Dry Mouth: 6.3%(3/48) vs 2.2%(1/46) Headache: 6.3%(3/48) vs 6.5%(3/46) Increase 1.0 BMI Point (Approx 6 lbs): 41.7%(20/48) vs 23.9%(11/46) Increased Appetite: 12.5%(6/48) vs 4.3%(2/46) Increased Perspiration: 2.1%(1/48) vs 2.2%(1/46) Nausea Or Vomiting: 4.2%(2/48) vs 4.3%(2/46) Nervousness: 14.6%(7/48) vs 6.5%(3/46) Palpitations: 0.0%(0/48) vs 0.0%(0/46) Sexual Difficulties: 6.3%(3/48) vs 6.5%(3/46) Skin Rash: 0.0%(0/48) vs 0.0%(0/46) Tiredness, Fatigue: 18.8%(9/48) vs 13.0%(6/46) Tremor: 0.0%(0/48) vs 0.0%(0/46)</p> <p>Withdrawals: Quetiapine vs Risperidone Withdrawals:70.8%(34/48) vs 69.6%(32/46) Withdrawals Due To Adverse Events:0.0%(0/48) vs 0.0%(0/46)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Analyzed: 14</p> <p>Method of AE assessment: Monitored</p>	<p>28, 35, 42, 49, 56 days</p>	
<p>Akerele et al. 2007²⁴⁷</p> <p>Substance abuse</p> <p>Olanzapine, Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry, Private</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 36</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: 76</p> <p>Eligible: 29</p> <p>Entering: 28</p> <p>Withdrawn: 12</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 16</p>	<p>Inclusion criteria: Diagnosis of schizophrenia or schizoaffective disorder, current cocaine and/or marijuana abuse/dependence, were using marijuana at least twice per week or cocaine at least once per week</p> <p>Exclusion criteria: Physiologically dependent on alcohol or other drugs, had unstable psychiatric symptomatology, unstable medical condition, enzyme function test greater than three times the upper limit of normal. A history of seizures/ neuroleptic malignant syndrome, not responded to either olanzapine or risperidone. Positive and negative symptom scale > 30.</p> <p>Interventions: Olanzapine 5-20 mg/days fixed titration schedule for 12 weeks vs Risperidone 3-9 mg/days fixed titration schedule for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 21, 28, 35, 42, 49, 56, 63, 70 days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Adverse Events: Olanzapine vs Risperidone Sedation: 57.1%(8/14) vs 78.6%(11/14) Worsening Of Abnormal Movements: 0.0%(0/14) vs 7.1%(1/14)</p> <p>Withdrawals: Olanzapine vs Risperidone Admitted To Inpatient Detox Unit Leading To Withdrawal:0.0%(0/14) vs 7.1%(1/14) Admitted To Inpatient Psych Unit Leading To Withdrawal:7.1%(1/14) vs 0.0%(0/14) Withdrawals:57.1%(8/14) vs 28.6%(4/14) Withdrawals Due To Adverse Events:0.0%(0/14) vs 0.0%(0/14)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Monitored		

AE=Adverse Event, NR=Not Reported

Quality

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Rainer et al. 2007 ¹⁴² Dementia/Agitation Quetiapine, Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Single blind, outcome assessment</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Sultz et al. 2008 ¹¹⁹ Dementia/Agitation Olanzapine, Quetiapine, Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Single blind, patient</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? No</p> <p>Was the care provider masked? No</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Maina et al. 2008 ¹⁹⁵ OCD Olanzapine, Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Single blind, outcome assessment If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Matsunaga et al. 2009 ¹⁹⁸ OCD Olanzapine, Quetiapine, Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Don't know Was the care provider masked? Don't know Were patients masked? Don't know	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Nejtek et al. 2008 ²⁵⁰ Substance abuse Quetiapine, Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Akerele et al. 2007 ²⁴⁷ Substance abuse Olanzapine, Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

AE= Adverse Event, NR=Not Reported

Active-Controlled Trials

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Correia Filho et al. 2005⁷⁸</p> <p>ADHD</p> <p>Risperidone</p> <p>Location: Latin America</p> <p>Trial: Not reported</p> <p>Funding source: Hospital, Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: African Ancestry, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 46 Withdrawn: 5 Lost to follow-up: 0 Analyzed: 41</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 6-16, MMR and ADHD, good health</p> <p>Exclusion criteria: PDD, schizophrenia or other psychotic disorder, seizure disorder requiring meds, history of head injury, previous treatment with MPH or risperidone, use of any other psych meds 1 month prior</p> <p>Interventions: MPH dosage not reported for 4 weeks vs Risperidone 0.5-4 mg/days flexible dose for 4 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression</p> <p>Timing of outcome assessment: 7, 14, 21, 28 days</p>	<p>Results: ADHD: Change in SNAP-IV Total Score (Total Score) at 4 weeks: Risperidone vs Methylphenidate - WMD = -6.00 (14.75 , 2.75)</p> <p>ADHD: Change in SNAP-IV Inattention (Inattention) at 4 weeks: Risperidone vs Methylphenidate - WMD = 1.20 (-1.91 , 4.31)</p> <p>ADHD: Change in SNAP-IV Hyperactivity (Hyperactivity) at 4 weeks: Risperidone vs Methylphenidate - WMD = -3.60 (-6.89 , -0.31)</p> <p>ADHD: Change in SNAP-IV OCD (OCD) at 4 weeks: Risperidone vs Methylphenidate - WMD = -1.80 (-5.02 , 1.42)</p> <p>Adverse Events: Methylphenidate Significant Difference Detected Between Baseline And End Point Scores In The SERs Total Scores: 0.0%(0/24) Risperidone Significant Difference Detected Between Baseline And End Point Scores On Any UKU Subscale Scores: 0.0%(0/22)</p> <p>Withdrawals: Methylphenidate vs Risperidone Galactorrhea (Led To withdrawal):0.0%(0/24) vs 4.5%(1/22) Vomiting (Led To withdrawal):4.2%(1/24) vs 0.0%(0/22) Withdrawals:8.3%(2/24) vs 13.6%(3/22) Withdrawals Due To Adverse Events:4.2%(1/24) vs 4.5%(1/22)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Prosser et al. 2009⁹⁶</p> <p>Anxiety</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 56</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 29</p> <p>Method of AE assessment: Not reported</p>	<p>Inclusion criteria: 21-55, history of panic attacks, disorder with panic attacks, HAM-A ≥ 17</p> <p>Exclusion criteria: Other Axis I, history of alcohol and substance abuse 6 month prior, use of antipsychotics 2 month prior, changes in antidepressant or mood stabilizer 2 month prior, other psychoactive meds, a history of adverse reaction to either risperidone or paroxetine</p> <p>Interventions: Paroxetine 30-40 mg/days flexible dose for 8 weeks vs Risperidone 0.125-1 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 3, 7, 14, 21, 28, 35, 42, 49, 56, 63 days</p>	<p>Results: Anxiety: Change in HAM-D-17 at 8 weeks: Risperidone vs Paroxetine - WMD = 0.65 (-4.73 , 6.03)</p> <p>Adverse Events: Paroxetine vs Risperidone Complained Of Adverse Events: 4.3%(1/23) vs 6.1%(2/33)</p> <p>Withdrawals: Paroxetine vs Risperidone Withdrawals:60.9%(14/23) vs 39.4%(13/33)</p>
<p>Moretti et al. 2005¹³²</p> <p>Dementia/Agitation</p> <p>Olanzapine</p>	<p>Inclusion criteria: MMSE at least 14 and DSM-IV for dementia. Probable VaD in accordance with the NINDS-AIREN 71-92</p> <p>Exclusion criteria:</p>	<p>Results: Dementia: Change in NPI total (Total) at 52 weeks: Haloperidol or promazine (typical neuroleptic) vs Olanzapine flexible dose - SMD = 0.38 (0.17 , 0.60)</p> <p>Adverse Events:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: CCT only</p> <p>Setting: Long-term care facilities</p> <p>Jadad: 0</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: 356 Entering: 346 Withdrawn: NR Lost to follow-up: 0 Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Normal pressure hydrocephalus. Previous psychiatric illness on central nervous system. Disorders and alcoholism</p> <p>Interventions: Typical antipsychotics 10 drops/day flexible dose for 12 months vs Olanzapine 2.5-7.5 mg/days flexible dose for 12 months</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 30, 91, 182, 274, 365 days</p>	<p>Typical neuroleptics (Group B) vs Olanzapine (Group A)</p> <p>Anger Episodes: 2.3%(4/173) vs 0.0%(0/173)</p> <p>Angina Pectoris Episode (Never Reported Before): 0.0%(0/173) vs 2.9%(5/173)</p> <p>Death From Complications Of A Thigh Bone Fracture Consequence Of A Fall: 0.6%(1/173) vs 0.0%(0/173)</p> <p>Death From Complications Of Pneumonia: 0.0%(0/173) vs 0.6%(1/173)</p> <p>Death From Myocardial Infarction: 0.6%(1/173) vs 0.6%(1/173)</p> <p>Death From Pulmonary Embolism (Had Suffered From Atrial Fibrillation): 0.6%(1/173) vs 0.0%(0/173)</p> <p>Diagnosed With Diabetes: 1.2%(2/173) vs 1.2%(2/173)</p> <p>Fall: 7.5%(13/173) vs 0.6%(1/173)</p> <p>Hospitalized For Myocardial Infarction: 1.2%(2/173) vs 0.0%(0/173)</p> <p>Inhalation Pneumonia: 1.7%(3/173) vs 0.0%(0/173)</p> <p>Nausea Associated With Anorexia: 19.7%(34/173) vs 0.0%(0/173)</p> <p>Oral Craving With A Weight Increase: 0.0%(0/173) vs 9.2%(16/173)</p> <p>Peripheral Arteriopathy: 0.0%(0/173) vs 0.6%(1/173)</p> <p>Renal Failure: 0.0%(0/173) vs 0.6%(1/173)</p> <p>Total Deaths: 1.7%(3/173) vs 1.2%(2/173)</p> <p>Transitory Sleepiness During Titration Phase: 24.9%(43/173) vs 23.1%(40/173)</p> <p>Weight Increase: 6.9%(12/173) vs 0.0%(0/173)</p> <p>Withdrawals: Typical neuroleptics (Group B) vs Olanzapine (Group A) Withdrawals:0.0%(0/173) vs 0.0%(0/173) Withdrawals Due To Adverse Events:0.0%(0/173) vs 0.0%(0/173)</p>
<p>Savaskan et al. 2006¹³³</p> <p>Dementia/Agitation</p> <p>Quetiapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: AD, behavioral symptoms > 65</p> <p>Exclusion criteria: Sensitivity to study drugs, medical illness, other antipsychotic</p> <p>Interventions: Haldol 0.5-4 mg/days fixed titration schedule for 5 weeks vs</p>	<p>Results: Dementia: Change in NPI agitation (Agitation) at 5 weeks: Haloperidol vs Quetiapine - SMD = 0.06 (-0.78 , 0.89)</p> <p>Dementia: Change in NPI total (Total) at 5 weeks: Haloperidol vs Quetiapine - SMD = 0.99 (0.10 , 1.88)</p> <p>Adverse Events: Haloperidol vs Quetiapine Arterial Hypertonia: 9.1%(1/11) vs 0.0%(0/11) EPS: 18.2%(2/11) vs 0.0%(0/11)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting, Inpatients, Hospitalized</p> <p>Jadad: 2</p> <p>Age: Mean: 68</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: 8 Lost to follow-up: 0 Analyzed: 22</p> <p>Method of AE assessment: Not reported</p>	<p>Quetiapine 25-200 mg/days fixed titration schedule for 5 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 35 days</p>	<p>Gastroenteritis: 0.0%(0/11) vs 9.1%(1/11) Infection Of Unknown Origin: 9.1%(1/11) vs 0.0%(0/11) Reversible Syncope: 0.0%(0/11) vs 9.1%(1/11)</p> <p>Withdrawals: Haloperidol vs Quetiapine Withdrawals Due To Adverse Events:18.2%(2/11) vs 18.2%(2/11)</p>
<p>Pollock et al. 2007¹³⁵</p> <p>Dementia/Agitation</p> <p>Risperidone</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Government, Private</p> <p>Design: RCT only</p>	<p>Inclusion criteria: AD, vascular dementia, dementia with Lewy bodies, mixed dementia or dementia not otherwise specified, need for hospitalization, >= 3 on agitation items and on psychosis items of NBRS</p> <p>Exclusion criteria: Schizophrenia, schizoaffective, delusional disorder, psychotic disorder, MR, cognitive deficits, delirium, Parkinson disease, substance dependence / abuse, MDD 6 month prior, >= 12 month CSDD, unstable physical illness, history of intolerance to citalopram or risperidone</p>	<p>Results: Dementia: Change in NBRS psy (Psychosis) at 12 weeks: Citalopram vs Risperidone - SMD = 0.06 (-0.33 , 0.44)</p> <p>Dementia: Change in NBRS ag (Agitation) at 12 weeks: Citalopram vs Risperidone - SMD = -0.11 (-0.50 , 0.28)</p> <p>Withdrawals: Citalopram vs Risperidone Bruising Leading To Withdrawal:1.9%(1/53) vs 0.0%(0/50) Elevated Liver Function Tests Leading To Withdrawal:0.0%(0/53) vs 2.0%(1/50) Gait Disturbance Leading To Withdrawal:1.9%(1/53) vs 6.0%(3/50) Gastrointestinal Bleeding Leading To Withdrawal:0.0%(0/53) vs 2.0%(1/50) Hypoglycemia Leading To Withdrawal:1.9%(1/53) vs 0.0%(0/50) Hypotension Leading To Withdrawal:0.0%(0/53) vs 2.0%(1/50)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Setting: Single setting</p> <p>Jadad: 5</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 111 Eligible: 106 Entering: 103 Withdrawn: 58 Lost to follow-up: 0 Analyzed: 45</p> <p>Method of AE assessment: Monitored</p>	<p>Interventions: Citalopram 10-40 mg/days flexible dose for 12 weeks vs Risperidone 0.5-2 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 3 days</p>	<p>Ileus Leading To Withdrawal:1.9%(1/53) vs 2.0%(1/50) Infection Leading To Withdrawal:3.8%(2/53) vs 0.0%(0/50) Intracranial Bleeding Leading To Withdrawal:0.0%(0/53) vs 2.0%(1/50) Other Extrapyramidal Symptoms (EPS) Leading To Withdrawal (Other Than Gait Disturbance):1.9%(1/53) vs 6.0%(3/50) Pneumonia Leading To Withdrawal:0.0%(0/53) vs 4.0%(2/50) Psychiatric Worsening: Increased Agitation Leading To Withdrawal:22.6%(12/53) vs 14.0%(7/50) Psychiatric Worsening: Onset Of Depression Leading To Withdrawal:1.9%(1/53) vs 0.0%(0/50) Psychiatric Worsening: Onset Of Psychosis Leading To Withdrawal:1.9%(1/53) vs 2.0%(1/50) Psychiatric Worsening: Readmission Leading To Withdrawal:3.8%(2/53) vs 6.0%(3/50) Psychiatric Worsening: Suicide Attempt Leading To Withdrawal:0.0%(0/53) vs 2.0%(1/50) Sedation Leading To Withdrawal:1.9%(1/53) vs 0.0%(0/50) Seizure Leading To Withdrawal:1.9%(1/53) vs 0.0%(0/50) Withdrawals:52.8%(28/53) vs 60.0%(30/50) Withdrawals Due To Adverse Events:7.5%(4/53) vs 18.0%(9/50)</p>
<p>Tariot et al. 2006¹²⁴</p> <p>Dementia/Agitation</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center, Long-term care facilities</p> <p>Jadad: 4</p> <p>Age: Mean: 83</p>	<p>Inclusion criteria: > 64 years old, not bedridden, nursing home residents for >= 2 weeks, diagnosed with DSM-IV AD, presence of psychosis, BPRS scores >=24, CGI-S scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPI-NH, scores of >= 5 on MMSE</p> <p>Exclusion criteria: Other clinically significant medical conditions, history of drug-induced agranulocytosis, acute orthostasis, clinically significant abnormal electrocardiogram, or concurrent other Axis I DSM-IV diagnosis.</p> <p>Interventions: Placebo for 10 weeks vs Haloperidol 0.5-12 mg/days flexible dose for</p>	<p>Results: Dementia: Change in NPI agitation (Agitation) at 10 weeks: Placebo vs Quetiapine - SMD = 0.25 (-0.05 , 0.54) Dementia: Change in NPI agitation (Agitation) at 10 weeks: Haloperidol vs Quetiapine - SMD = 0.04 (-0.26 , 0.34) Dementia: Change in NPI total (Total) at 10 weeks: Placebo vs Quetiapine - SMD = 0.01 (-0.29 , 0.30) Dementia: Change in NPI total (Total) at 10 weeks: Haloperidol vs Quetiapine - SMD = -0.31 (-0.61 , -0.01)</p> <p>Adverse Events: Haloperidol vs Quetiapine vs Placebo Abnormal Gait: 10.6%(10/94) vs 3.3%(3/91) vs 3.0%(3/99) Accidental Injury Total: 45.7%(43/94) vs 40.7%(37/91) vs 42.4%(42/99) Agitation: 13.8%(13/94) vs 7.7%(7/91) vs 21.2%(21/99) Convulsion: 0.0%(0/94) vs 4.4%(4/91) vs 0.0%(0/99) Deaths: 7.4%(7/94) vs 2.2%(2/91) vs 4.0%(4/99) Dyspepsia: 4.3%(4/94) vs 0.0%(0/91) vs 4.0%(4/99) Falls: 28.7%(27/94) vs 28.6%(26/91) vs 28.3%(28/99) Fever: 11.7%(11/94) vs 3.3%(3/91) vs 6.1%(6/99) Fractures: 6.4%(6/94) vs 2.2%(2/91) vs 7.1%(7/99)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 501 Eligible: 284 Entering: 284 Withdrawn: 103 Lost to follow-up: 1 Analyzed: 180</p> <p>Method of AE assessment: Monitored</p>	<p>10 weeks vs Quetiapine 25-600 mg/days flexible dose for 10 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 48 hour(s). Patients still eligible after washout were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 42, 56, 70 days</p>	<p>Infection: 5.3%(5/94) vs 14.3%(13/91) vs 5.1%(5/99) Insomnia: 5.3%(5/94) vs 0.0%(0/91) vs 1.0%(1/99) Nonserious Cerebrovascular Event: 0.0%(0/94) vs 1.1%(1/91) vs 3.0%(3/99) Pain: 9.6%(9/94) vs 13.2%(12/91) vs 11.1%(11/99) Pallor: 4.3%(4/94) vs 0.0%(0/91) vs 0.0%(0/99) Pharyngitis: 4.3%(4/94) vs 5.5%(5/91) vs 10.1%(10/99) Rash: 12.8%(12/94) vs 13.2%(12/91) vs 13.1%(13/99) Serious AEs: 16.0%(15/94) vs 11.0%(10/91) vs 12.1%(12/99) Somnolence, All: 36.2%(34/94) vs 25.3%(23/91) vs 4.0%(4/99) Somnolence, Serious: 1.1%(1/94) vs 1.1%(1/91) vs 0.0%(0/99) Urinary Incontinence: 4.3%(4/94) vs 4.4%(4/91) vs 0.0%(0/99) Urinary Tract Infection: 10.6%(10/94) vs 12.1%(11/91) vs 5.1%(5/99) Vomiting: 6.4%(6/94) vs 12.1%(11/91) vs 5.1%(5/99)</p> <p>Withdrawals: Haloperidol vs Quetiapine vs Placebo Somnolence Leading To Withdrawal: 3.2%(3/94) vs 1.1%(1/91) vs 0.0%(0/99) Withdrawals: 41.5%(39/94) vs 31.9%(29/91) vs 36.4%(36/99) Withdrawals Due To Adverse Events: 18.1%(17/94) vs 11.0%(10/91) vs 13.1%(13/99)</p>
<p>Verhey et al. 2006¹³⁶</p> <p>Dementia/Agitation</p> <p>Olanzapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Multi-center, Long-term care facilities</p> <p>Jadad: 3</p> <p>Age: Mean: 70</p>	<p>Inclusion criteria: Age >= 60 years, diagnosis of dementia according to DSM-IV, agitation level requiring antipsychotic treatment, no use of antipsychotic treatment within 3 days of inclusion CMAI score >=45</p> <p>Exclusion criteria: Delirium, neurological conditions that could contribute to psychosis or dementia.</p> <p>Interventions: Haloperidol 1-3 mg/days flexible dose for 5 weeks vs Olanzapine 2.5-7.5 mg/days flexible dose for 5 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 3-11 day(s). Patients still eligible after washout were randomized.</p>	<p>Results: Dementia: Change in CMAI (Agitation) at 5 weeks: Haloperidol vs Olanzapine - SMD = -0.21 (-0.73 , 0.31) Dementia: Change in NPI psy (Psychosis) at 5 weeks: Haloperidol vs Olanzapine - SMD = -0.03 (-0.57 , 0.50) Dementia: Change in NPI total (Total) at 5 weeks: Haloperidol vs Olanzapine - SMD = -0.18 (-0.77 , 0.41)</p> <p>Adverse Events: Haloperidol vs Olanzapine Accommodation Disturbances: 25.0%(7/28) vs 10.0%(3/30) Akathisia: 21.4%(6/28) vs 13.3%(4/30) Asthenia/Lassitude/Fatigue: 78.6%(22/28) vs 60.0%(18/30) Changes Of Sexual Functions: 10.7%(3/28) vs 13.3%(4/30) Concentration Difficulties: 75.0%(21/28) vs 80.0%(24/30) Constipation: 32.1%(9/28) vs 20.0%(6/30) Depression: 71.4%(20/28) vs 56.7%(17/30) Diarrhea: 17.9%(5/28) vs 26.7%(8/30) Dystonia: 14.3%(4/28) vs 13.3%(4/30) Emotional Indifference: 57.1%(16/28) vs 33.3%(10/30) Failing Memory: 100.0%(28/28) vs 96.7%(29/30) Headache: 32.1%(9/28) vs 23.3%(7/30)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: 9 Lost to follow-up: 0 Analyzed: NR</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 35 days</p>	<p>Hyperkinesia: 14.3%(4/28) vs 20.0%(6/30) Hypokinesia/akinesia: 35.7%(10/28) vs 30.0%(9/30) Increased Dream Activity: 7.1%(2/28) vs 13.3%(4/30) Increased Duration Of Sleep: 42.9%(12/28) vs 63.3%(19/30) Increased Salivation: 25.0%(7/28) vs 13.3%(4/30) Increased Tendency To Sweating: 14.3%(4/28) vs 16.7%(5/30) Micturition Disturbances: 25.0%(7/28) vs 20.0%(6/30) Nausea/Vomiting: 28.6%(8/28) vs 23.3%(7/30) Orthostatic Dizziness: 28.6%(8/28) vs 16.7%(5/30) Palpitations/Tachycardia: 3.6%(1/28) vs 10.0%(3/30) Paraesthesias: 7.1%(2/28) vs 6.7%(2/30) Polyuria/Polydipsia: 17.9%(5/28) vs 16.7%(5/30) Pruritus: 21.4%(6/28) vs 10.0%(3/30) Rash: 21.4%(6/28) vs 13.3%(4/30) Reduced Duration Of Sleep: 32.1%(9/28) vs 36.7%(11/30) Reduced Salivation: 14.3%(4/28) vs 10.0%(3/30) Rigidity: 46.4%(13/28) vs 30.0%(9/30) Sleepiness/Sedation: 78.6%(22/28) vs 60.0%(18/30) Tension/Inner Unrest: 82.1%(23/28) vs 80.0%(24/30) Tremor: 25.0%(7/28) vs 26.7%(8/30) Weight Gain: 25.0%(7/28) vs 20.0%(6/30) Weight Loss: 10.7%(3/28) vs 13.3%(4/30)</p> <p>Withdrawals: Haloperidol vs Olanzapine Withdrawals:0.0%(0/28) vs 10.0%(3/30)</p>
<p>Holmes et al. 2007¹³⁷</p> <p>Dementia/Agitation</p> <p>Risperidone</p> <p>Location: Not reported</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p>	<p>Inclusion criteria: Severe probable AD, MMSE <6, NINCDS-ADRD and CMAI >3 p for at least 6 weeks, nursing home</p> <p>Exclusion criteria: Previous exposure at a cholinesterase inhibitor or had ever received psychotropic drugs of greater than 20mg thioridazine (or its equivalent).</p> <p>Interventions: Other, Rivastigmine 3-6 mg/days fixed titration schedule for 6 weeks vs</p>	<p>Results: Dementia: Change in CMAI (Agitation) at 6 weeks: Rivastigmine vs Risperidone - SMD = 1.31 (0.47 , 2.15)</p> <p>Adverse Events: Risperidone vs Rivastigmine Any Adverse Event: 33.3%(4/12) vs 60.0%(9/15) Cellulitis: 8.3%(1/12) vs 0.0%(0/15) Chest Infection: 8.3%(1/12) vs 6.7%(1/15) Constipation: 8.3%(1/12) vs 6.7%(1/15) Nausea And Vomiting: 0.0%(0/12) vs 20.0%(3/15) Persistent Agitation: 8.3%(1/12) vs 20.0%(3/15) Skin Rash: 0.0%(0/12) vs 6.7%(1/15) Transient Ischemic Attack: 8.3%(1/12) vs 0.0%(0/15)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Setting: Long-term care facilities</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 70 Eligible: 28 Entering: 27 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Risperidone 0.5 mg/days fixed titration schedule for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 42 days</p>	
<p>Mowla et al. 2010¹³⁸</p> <p>Dementia/Agitation</p> <p>Risperidone</p> <p>Location: Middle East</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Not reported</p>	<p>Inclusion criteria: AD per DSM-IV of mild to moderate severity, behavioral disturbance, NPI part 1 > 1 in subitems related to delusions, hallucinations, agitation / aggression and irritability / liability.</p> <p>Exclusion criteria: Dementia of other etiology, organic disease, other psychiatric disorders, medication in past 4 weeks.</p> <p>Interventions: Other, 32 (Topiramate) 44.04 mg/days flexible dose for 8 weeks vs Risperidone 1.9 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p>	<p>Results: Dementia: Change in NPI total (Total) at 8 weeks: Topiramate vs Risperidone - SMD = 0.23 (-0.38 , 0.85)</p> <p>Dementia: Change in CMAI (Agitation) at 8 weeks: Topiramate vs Risperidone - SMD = 0.06 (-0.56 , 0.67)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 48</p> <p>Withdrawn: 7</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 41</p> <p>Method of AE assessment: Elicited by investigator</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 42, 56 days</p>	
<p>Doree et al. 2007¹⁷⁵</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p>	<p>Inclusion criteria: 18 - 65, MDD without psychotic features, HAMD >= 20, CGI >= 4 despite antidepressants at max dose + >=4 weeks</p> <p>Exclusion criteria: Bipolar or other Axis I, substance dependence within 6 months, unstable medical condition</p> <p>Interventions: Lithium 600-vario mg/days flexible dose for 8 weeks vs Quetiapine 25-600 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56 days</p>	<p>Results: Depression: Change in MADRS at 8 weeks: Quetiapine vs Lithium - WMD = -10.90 (-16.47 , -5.33)</p> <p>Adverse Events: Lithium Tremor: 60.0%(6/10) Quetiapine Somnolence: 50.0%(5/10) Quetiapine vs Lithium Serious Adverse Event: 0.0%(0/10) vs 0.0%(0/10)</p> <p>Withdrawals: Quetiapine vs Lithium Mixed State Resulting In Withdrawal:0.0%(0/10) vs 10.0%(1/10) Tremor And Nausea Resulting In Withdrawal:0.0%(0/10) vs 10.0%(1/10) Withdrawals:0.0%(0/10) vs 30.0%(3/10) Withdrawals Due To Adverse Events:0.0%(0/10) vs 20.0%(2/10)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Entering: 20 Withdrawn: 3 Lost to follow-up: 0 Analyzed: 17</p> <p>Method of AE assessment: Monitored</p>		
<p>Hussain et al. 2005¹⁷⁷</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: NR</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: 18 Lost to follow-up: 0 Analyzed: NR</p> <p>Method of AE assessment: NR</p>	<p>Inclusion criteria: Diagnosed with MDD using DSM-IV criteria</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Paroxetine dosage not reported for duration not reported vs Venlafaxine dosage not reported for duration not reported vs Quetiapine, Paroxetine dosage not reported for duration not reported vs Quetiapine, Venlafaxine dosage not reported for duration not reported</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 21, 42, 84, 182, 365, 730, 1094 days</p>	<p>Results: Depression: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Mondraty et al. 2005¹⁸¹</p> <p>Eating disorder</p> <p>Olanzapine</p> <p>Location: Australia/New Zealand</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Mean: 25</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: 26 Eligible: 15 Entering: 15 Withdrawn: 0 Lost to follow-up: 0 Analyzed: 15</p> <p>Method of AE assessment: Not reported</p>	<p>Inclusion criteria: Fulfilling DSM-IV criteria for anorexia nervosa</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Chlorpromazine 25-100 mg/days flexible dose for duration not reported vs Olanzapine 5-15 mg/days flexible dose for variable duration</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 46 days</p>	<p>Results: Eating Disorder: Change in BMI at 2 weeks: Olanzapine vs Chlorpromazine - WMD = 0.50 (-1.49 , 2.49)</p> <p>Adverse Events: Chlorpromazine vs Olanzapine Blurring Of Vision And Postural Hypotension: 14.3%(1/7) vs 0.0%(0/8) Sedation: 42.9%(3/7) vs 12.5%(1/8)</p>
<p>Diniz et al. 2009²⁰⁰</p> <p>OCD</p> <p>Quetiapine</p>	<p>Inclusion criteria: 18-65, OCD, treatment failure to SSRI</p> <p>Exclusion criteria: Substance dependence or abuse, psychosis,</p>	<p>Results: OCD: Change in YBOCS (Total Score) at 12 weeks: Quetiapine vs Clomipramine - WMD = -3.60 (9.27 , 2.07)</p> <p>Adverse Events:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: Brazil</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 2</p> <p>Age: Mean: 20</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 48 Eligible: 35 Entering: 31 Withdrawn: 13 Lost to follow-up: NR Analyzed: 18</p> <p>Method of AE assessment: Monitored</p>	<p>suicide risk, pregnant / intending to become pregnant</p> <p>Interventions: Clomipramine 25-75 mg/days flexible dose for 12 weeks vs Quetiapine 50-200 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Run-in: Fluoxetine for 12 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 28, 56, 84 days</p>	<p>Clomipramine vs Quetiapine Severe Adverse Events: 0.0%(0/15) vs 0.0%(0/16) Quetiapine 3 Symptoms Of Serotonergic Syndrome (Excessive Sweating, Tremors And Motor Agitation) Leading To Being Dropped: 0.0%(0/16)</p> <p>Withdrawals: Clomipramine 3 Symptoms Of Serotonergic Syndrome (Excessive Sweating, Tremors And Motor Agitation) Leading To Withdrawal:6.7%(1/15) Clomipramine vs Quetiapine Withdrawals:40.0%(6/15) vs 43.8%(7/16) Withdrawals Due To Adverse Events:40.0%(6/15) vs 43.8%(7/16)</p>
<p>Shafti et al. 2010²²⁵</p> <p>Personality disorder</p> <p>Olanzapine</p> <p>Location: Middle East</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p>	<p>Inclusion criteria: BPD per DSM-IV-TR</p> <p>Exclusion criteria: Prominent comorbid mental disorder</p> <p>Interventions: Other, Haldol 6.83 mg/days flexible dose for 8 weeks vs Olanzapine 7.08 mg/days flexible dose for 8 weeks</p>	<p>Results: Personality Disorder: Change in BDHI at 8 weeks: Olanzapine vs Haliperidol - WMD = -3.79 (-11.51 , 3.93)</p> <p>Personality Disorder: Change in BPRS at 8 weeks: Olanzapine vs Haliperidol - WMD = 5.31 (-11.31 , 9.51)</p> <p>Personality Disorder: Change in CGI-S at 8 weeks: Olanzapine vs Haliperidol - WMD = 0.41 (-0.97 , 0.65)</p> <p>Adverse Events: Haloperidol vs Olanzapine</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 4</p> <p>Age: Mean: 30</p> <p>Sex: 100% Female</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 28</p> <p>Withdrawn: 0</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 28</p> <p>Method of AE assessment: Monitored</p>	<p>Run-in/wash-out period: Wash-out: Psychotropics for 7 day(s) were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 56 days</p>	<p>Extrapyramidal Symptoms Not Resulting In Prescription Of Anticholinergics: 0.0%(0/14) vs 14.3%(2/14)</p> <p>Extrapyramidal Symptoms Resulting In Prescription Of Anticholinergics: 50.0%(7/14) vs 0.0%(0/14)</p> <p>Tremor, Parkinsonism, And Akathisia: 57.1%(8/14) vs 0.0%(0/14)</p> <p>Weight Gain, Somnolence, Dizziness And Tremor: 0.0%(0/14) vs 42.9%(6/14)</p> <p>Withdrawals: Haloperidol vs Olanzapine Withdrawals:0.0%(0/14) vs 0.0%(0/14) Withdrawals Due To Adverse Events:0.0%(0/14) vs 0.0%(0/14)</p>
<p>Rubio et al. 2006²⁴²</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Unclear</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p>	<p>Inclusion criteria: Male, 18-65, schizophrenia and SUD for substances other than caffeine and nicotine.</p> <p>Exclusion criteria: Organic or neurological disorder, other psychotic disorder, abnormal labs on ECG</p> <p>Interventions: Other, Zuclopenthixol 10-100 mg/days frequency not reported for 6 months vs Risperidone 3-12 mg/days frequency not reported for 6 months</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities:</p>	<p>Results: Substance Abuse: Cross over study</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Age: Not reported</p> <p>Sex: 100% Male</p> <p>Race: Not reported</p> <p>Screened: 124 Eligible: NR Entering: 66 Withdrawn: 4 Lost to follow-up: 0 Analyzed: 62</p> <p>Method of AE assessment: Monitored</p>	<p>None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	
<p>Gerra et al. 2006²⁷³</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Government, Professional association</p> <p>Design: CCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p>	<p>Inclusion criteria: Heroin dependent patients entering methadone and buprenorphine, aggressive personality traits.</p> <p>Exclusion criteria: > 3 month of drugs other than heroin or > 6 month alcohol dependent, severe chronic liver illness, renal diseases, other chronic medical disorders, recent significant weight loss, obesity, endocrinotherapy, immune deficiency. A comorbidity of schizophrenia or bipolar disorder > 60 BDHI.</p> <p>Interventions: SRI and Antidepressant Fluoxetine mean 25.26 (SD 5.9) ; Paroxetine mean 22.5 (SD 6.8); Clonazepam mean 5.15 (SD 1.67) for 12 weeks vs Olanzapine mean 12.1 (SD 5.4) for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p>	<p>Results: Substance Abuse: Change in BDHI at 12 weeks: Olanzapine+Methadone/Buprenorphine vs SSRIs+Clonazepam+Methadone/Buprenorphine - WMD = -10.26 (-11.00 , -9.52)</p> <p>Adverse Events: Fluoxetine/paroxetine and clonazepam vs Olanzapine Overt BDZs Abuse With Severe Sedation And Paradoxical Symptoms That Contributed To Drop-Out: 11.4%(4/35) vs 0.0%(0/32) Paradoxical Effects With Agitation, Increased Irritability, Negativism And The Tendency To Clonazepam Abuse: 20.0%(7/35) vs 0.0%(0/32) Significant Changes Of Glucose Plasma Levels: 0.0%(0/35) vs 0.0%(0/32) Olanzapine Weight Gain =7%: 12.5%(4/32)</p> <p>Withdrawals: Fluoxetine/paroxetine and clonazepam vs Olanzapine Withdrawals:45.7%(16/35) vs 46.9%(15/32)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 67</p> <p>Entering: 67</p> <p>Withdrawn: 34</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 33</p> <p>Method of AE assessment: Not reported</p>	<p>Comorbidities: OCD, Personality Disorder</p> <p>Timing of outcome assessment: 84 days</p>	
<p>Gerra et al. 2007²⁴⁸</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: CCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 61</p> <p>Entering: 61</p>	<p>Inclusion criteria: Heroin dependent, entering methadone and buprenorphine long-term treatment, SSDS (schizophrenia spectrum disorder) treated with olanzapine or haloperidol.</p> <p>Exclusion criteria: Long lasting period of consumption of drugs, other than heroin (3 months) or prolonged alcohol dependence (6 months), severe chronic liver illness, renal disease, other medial chronic disorders, recent significant weight loss / obesity endocrine and immune deficiency.</p> <p>Interventions: Haloperidol dosage not reported for 12 weeks vs Olanzapine dosage not reported for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: OCD, Personality Disorder</p> <p>Timing of outcome assessment: 84 days</p>	<p>Results: Substance Abuse: Change in Retention Rate at 12 weeks: olanzapine vs Haloperidol - RR = 2.72 (0.84 , 8.79)</p> <p>Adverse Events: Haloperidol vs Olanzapine Anticholinergic Drugs Prescribed To Treat This Many Pts With Extrapyramidal Symptoms: 15.4%(4/26) vs 0.0%(0/35) Extrapyramidal Symptoms (Akathisia, Dystonia, And Tardive Dyskinesia With Restlessness And Objective Motor Signs, Difficulty In Opening The Eyelids, Torticollis, And Oculogyric Crisis): 26.9%(7/26) vs 0.0%(0/35) Persistent Sedation And Tiredness: 69.2%(18/26) vs 0.0%(0/35) Significant Changes Of Glucose Plasma Levels: 0.0%(0/26) vs 0.0%(0/35) Weight Gain =7%: 0.0%(0/26) vs 17.1%(6/35)</p> <p>Withdrawals: Haloperidol vs Olanzapine Withdrawals:50.0%(13/26) vs 8.6%(3/35)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Withdrawn: 16 Lost to follow-up: 8 Analyzed: 35</p> <p>Method of AE assessment: Not reported</p>		
<p>Green et al. 2004²⁴⁹</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US, Canada, Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Mean: 16</p> <p>Sex: 80-99% Male</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: 263 Entering: NR Withdrawn: NR Lost to follow-up: 1 Analyzed: 262</p>	<p>Inclusion criteria: Schizophrenia, schizoaffective, disorder / schizophreniform disorder according to DSM-IV SCID-IV > 2 items of >= 4 or one >= 5 and CGI >= 4 / PANSS</p> <p>Exclusion criteria: Psychotic longer than 5 years. Recovery from initial episode for 6 months or longer. Treated with an injectable depot neuroleptic within 3 month. PSM-IV substance dependence within 1 month.</p> <p>Interventions: Haldol 2-20 mg/days flexible dose for 12 weeks vs Olanzapine 5-20 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 56, 70 days</p>	<p>Results: Substance Abuse: Not all patients had Substance Use Disorder,</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Martinotti et al. 2009²⁵¹</p> <p>Substance abuse</p> <p>Aripiprazole</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Mean: 40</p> <p>Sex: 80-99% Male</p> <p>Race: Not reported</p> <p>Screened: 112</p> <p>Eligible: 57</p> <p>Entering: 57</p> <p>Withdrawn: 3</p> <p>Lost to follow-up: 11</p> <p>Analyzed: 43</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Alcohol use disorders \geq 3 years, daily alcohol intake \geq 6 units, alcohol dependence, declared commitment to the goal of total abstinence</p> <p>Exclusion criteria: Severe physical illness or mental disorders, regularly taking anticonvulsants, antidepressants or antipsychotics, pregnant, history of severe AE to aripiprazole or naltrexone, previous treated with ARI or NAL.</p> <p>Interventions: Naltrexone 10-50 mg/days fixed titration schedule for 16 weeks vs Aripiprazole 5-15 mg/days flexible dose for 16 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Personality Disorder, Substance Abuse, Eating Disorder</p> <p>Timing of outcome assessment: 14, 56, 112 days</p>	<p>Results: Substance Abuse: Change in Complete Abstinence (Alcohol) at 16 weeks: Aripiprazole vs Naltrexone - RR = 1.05 (0.56 , 1.98)</p> <p>Substance Abuse: Change in Abstinent Days (Alcohol) at 16 weeks: Aripiprazole vs Naltrexone - SMD = 0.13 (-0.39 , 0.65)</p> <p>Adverse Events: Aripiprazole vs Naltrexone Akathisia: 6.9%(2/29) vs 0.0%(0/28) Confusion: 3.4%(1/29) vs 0.0%(0/28) Dizziness: 0.0%(0/29) vs 7.1%(2/28) Euphoria: 6.9%(2/29) vs 0.0%(0/28) Hypothension: 0.0%(0/29) vs 10.7%(3/28) Nausea And Vomiting: 10.3%(3/29) vs 21.4%(6/28)</p> <p>Withdrawals: Aripiprazole vs Naltrexone Withdrawals:75.9%(22/29) vs 75.0%(21/28) Withdrawals Due To Adverse Events:6.9%(2/29) vs 17.9%(5/28)</p>
<p>Rubio et al. 2006²⁴³</p> <p>Substance abuse</p> <p>Risperidone</p>	<p>Inclusion criteria: 18-65, schizophrenia and SUD for substances other than caffeine and nicotine, according to DSM-IV.</p> <p>Exclusion criteria:</p>	<p>Results: Substance Abuse: Change in Number of Positive Uring Tests at 24 weeks: Risperidone vs Zuclopenthixol - WMD = 1.69 (0.58 , 2.80)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source:</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 1</p> <p>Age: Mean: 35</p> <p>Sex: 80-99% Male</p> <p>Race: Not reported</p> <p>Screened: 183 Eligible: 115 Entering: 115 Withdrawn: NR Lost to follow-up: NR Analyzed: 106</p> <p>Method of AE assessment: Monitored</p>	<p>Clinically significant organic or neurologic disorder, serious psychotic disorder other than schizophrenia, clinically relevant abnormalities</p> <p>Interventions: Other, Zuclopenthixol 10-50 mg/days flexible dose for 6 weeks vs Risperidone 2-6 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 days</p>	
<p>Sayers et al. 2005²⁴⁴</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p>	<p>Inclusion criteria: Schizophrenia and cocaine abuse in last 6 month. 18-60</p> <p>Exclusion criteria: Use of depot meds within 6 month, history of sensitization to haldol or olanzapine or history of NMS, pregnant, lactating, unstable medical problems</p> <p>Interventions: Haldol 5-20 mg/days flexible dose for 26 weeks</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Haloperidol Withdrawals:41.7%(5/12)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Design: RCT only</p> <p>Setting: Single setting, VA Healthcare System</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry</p> <p>Screened: 170 Eligible: 24 Entering: 24 Withdrawn: NR Lost to follow-up: NR Analyzed: 14</p> <p>Method of AE assessment: Monitored</p>	<p>vs Olanzapine 5-20 mg/days flexible dose for 26 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 days</p>	
<p>Smelson et al. 2006²⁴⁵</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: VA Healthcare System</p>	<p>Inclusion criteria: Cocaine dependence and schizophrenia, positive change in baseline craving after cocaine cues</p> <p>Exclusion criteria: Other AXIS I disorders, taking other CNS (central nervous system) meds (medications), history of seizures, pregnant, chronic CNS disease other than schizophrenia</p> <p>Interventions: Haldol 5-20 mg/days flexible dose for 6 weeks</p> <p>vs Olanzapine 5-20 mg/days flexible dose for 6 weeks</p>	<p>Results: Substance Abuse: Change in Voris Cocaine Craving Questionnaire (Craving Intensity Scor at 6 weeks: Olanzapine vs Haloperidol - WMD = -6.30 (-17.35 , 4.75)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 31 Withdrawn: NR Lost to follow-up: NR Analyzed: 18</p> <p>Method of AE assessment: Not applicable</p>	<p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 42 days</p>	
<p>Tsuang et al. 2002²⁴⁶</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: CCT only</p> <p>Setting: VA Healthcare System</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p>	<p>Inclusion criteria: Cocaine abusing outpatient with schizophrenia</p> <p>Exclusion criteria:</p> <p>Interventions: Olanzapine 15-20 mg/days frequency not reported for duration not reported vs Haldol 5-10 mg/days frequency not reported for duration not reported</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Haloperidol Withdrawals:100.0%(2/2)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Not reported</p> <p>Screened: NR Eligible: 4 Entering: 23 Withdrawn: 1 Lost to follow-up: 1 Analyzed: 3</p> <p>Method of AE assessment: Not reported</p>		

AE=Adverse Event, NR=Not Reported

Quality

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Correia Filho et al. 2005 ⁷⁸ ADHD Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Single blind, not described</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Don't know</p> <p>Was the care provider masked? Don't know</p> <p>Were patients masked? Don't know</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Prosser et al. 2009 ⁹⁶ Anxiety Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Single blind, outcome assessment</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Moretti et al. 2005 ¹³² Dementia/Agitation Olanzapine	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Yes	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Savaskan et al. 2006 ¹³³ Dementia/Agitation Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Pollock et al. 2007 ¹³⁵ Dementia/Agitation Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Yes	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Tariot et al. 2006 ¹²⁴ Dementia/Agitation Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Verhey et al. 2006 ¹³⁶ Dementia/Agitation Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Holmes et al. 2007 ¹³⁷ Dementia/Agitation Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Yes	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Mowla et al. 2010 ¹³⁸ Dementia/Agitation Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Doree et al. 2007 ¹⁷⁵ Depression Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Open</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? No</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Hussain et al. 2005 ¹⁷⁷ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Don't know Was the care provider masked? Don't know Were patients masked? Don't know	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Mondraty et al. 2005 ¹⁸¹ Eating disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Don't know

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Diniz et al. 2009 ²⁰⁰ OCD Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Open</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? No</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Shafti et al. 2010 ²²⁵ Personality disorder Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Rubio et al. 2006 ²⁴² Substance abuse Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Yes Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Gerra et al. 2006 ²⁷³ Substance abuse Olanzapine	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Yes	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Gerra et al. 2007 ²⁴⁸ Substance abuse Olanzapine	<p>Was the study described as randomized? No</p> <p>Was the method of randomization adequate? No</p> <p>Was the treatment allocation concealed? No</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Open</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? No</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Green et al. 2004 ²⁴⁹ Substance abuse Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
<p>Hutchison et al. 2003²⁵⁵</p> <p>Substance abuse</p> <p>Olanzapine</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Yes</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
<p>Martinotti et al. 2009²⁵¹</p> <p>Substance abuse</p> <p>Aripiprazole</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Rubio et al. 2006 ²⁴³ Substance abuse Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? No</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Open</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Sayers et al. 2005 ²⁴⁴ Substance abuse Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Smelson et al. 2006 ²⁴⁵ Substance abuse Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Tsuang et al. 2002 ²⁴⁶ Substance abuse Olanzapine	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Don't know	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? No Was the outcome assessment timing similar in all groups? No

AE=Adverse Events, NR=Not Reported

Augmentation Trials

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Zeni et al. 2009⁸⁰</p> <p>ADHD</p> <p>Aripiprazole</p> <p>Location: Latin America</p> <p>Trial: Not reported</p> <p>Funding source: Government, Hospital</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Mean: 8</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 710 Eligible: 16 Entering: 16 Withdrawn: 1 Lost to follow-up: 0 Analyzed: 15</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Inclusion criteria: Age 8-17, diagnosed borderline personality disorder co-morbid ADHD \geq 30% improvement in mood symptoms in the previous trial of ARI, SNAP-IV score \geq 1.5</p> <p>Exclusion criteria: IQ < 70, use of medication besides ARI 10 weeks before entering study, pervasive developmental disorder, schizophrenia, substance abuse, suicidal, hypersensitive to ARI / MPH, pregnancy, acute or chronic disease</p> <p>Interventions: Aripiprazole 5-20 mg/days fixed single dose for 2 weeks vs Aripiprazole, Methylphenidate 5-20 mg/days fixed single dose for 2 weeks</p> <p>Run-in/wash-out period: Run-in: Aripiprazole plus placebo for 12 week(s). Patients who met the study criteria were randomized.</p> <p>Comorbidities: Anxiety</p> <p>Timing of outcome assessment: 7, 14 days</p>	<p>Results: ADHD: Cross over study</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Khan et al.⁹¹</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Paladum (D1440L00016)</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 409</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Inclusion criteria: 18-65 years old, GAD, HAM-A \geq 20, HAM-A item 1 and 2 \geq 2, CGI-S \geq 4, inadequate response to SSRI</p> <p>Exclusion criteria: DSM-IV Axis disorders other than GAD, schizophrenia or other psychotic disorders, depression, MADRS item 10 score \geq 4, substance abuse, pregnant, severe illness, ECG significant</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 174.3 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: Placebo for 1 week(s). Patients who met the study criteria were randomized. In Wash-out: Psychotropics for 28 day(s) were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56 days</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 8 weeks: Quetiapine+SSRI vs Placebo + SSRI - RR = 2.00 (0.68 , 5.85)</p> <p>Adverse Events: Placebo + antidepressant Mads Item 10 (Suicidal Thoughts) Score Of =5: 0.0%(0/200) Placebo + antidepressant vs Quetiapine XR + antidepressant Ae Potentially Related To Suicidality: 0.0%(0/200) vs 0.0%(0/209) Aes Potentially Related To Extrapyramidal Symptoms: 2.0%(4/200) vs 3.8%(8/209) Aes Potentially Related To Sexual Dysfunction: 0.0%(0/200) vs 2.9%(6/209) Aes Potentially Related To Somnolence/Sedation: 14.5%(29/200) vs 35.9%(75/209) Concomitant Anxiolytics: Snris: 27.5%(55/200) vs 26.3%(55/209) Concomitant Anxiolytics: Ssrri: 73.5%(147/200) vs 76.6%(160/209) Constipation: 3.9%(8/207) vs 6.0%(13/216) Dizziness: 4.4%(9/204) vs 10.3%(22/213) Dry Mouth: 7.5%(15/200) vs 23.4%(49/209) Fatigue: 3.9%(8/205) vs 9.3%(20/214) Headache: 10.3%(21/203) vs 11.3%(24/212) Incidence Of Aes: 60.0%(120/200) vs 73.7%(154/209) Increased Qtc Interval: 0.0%(0/200) vs 0.0%(0/209) Insomnia: 1.5%(3/206) vs 7.0%(15/215) Insomnia During 8 Week F/Up Period: 0.0%(0/210) vs 4.6%(10/219) Nasopharyngitis: 8.1%(17/209) vs 3.2%(7/218) Nausea: 5.8%(12/208) vs 5.5%(12/217) Nausea During 8 Week F/Up Period: 0.9%(2/211) vs 2.3%(5/220) Patients Experiencing A =7% Increase In Weight: 1.0%(2/200) vs 4.3%(9/209) Saes: 0.0%(0/200) vs 0.0%(0/209) Sedation: 2.5%(5/202) vs 12.3%(26/211) Sedation Leading To Discontinuation: 0.0%(0/200) vs 5.3%(11/209) Somnolence: 11.9%(24/201) vs 22.4%(47/210) Somnolence Leading To Discontinuation: 0.0%(0/200) vs 2.9%(6/209) Quetiapine XR + antidepressant Mads Item 10 (Suicidal Thoughts) Score Of =4: 0.0%(0/209)</p> <p>Withdrawals: Placebo + antidepressant vs Quetiapine XR + antidepressant Withdrawals Due To Adverse Events:2.0%(4/200) vs 11.5%(24/209)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>McIntyre et al. 2007⁸⁶</p> <p>Anxiety, Depression</p> <p>Quetiapine</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 73</p> <p>Eligible: 58</p> <p>Entering: 58</p> <p>Withdrawn: 22</p> <p>Lost to follow-up: 2</p> <p>Analyzed: 34</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-65, major depression, HAM-D 17 >= 18, CGI-S >=4, HAM-A >= 14, treated with single SSRI/venlafaxine at a therapeutic dose >= 6 weeks</p> <p>Exclusion criteria: Substance abuse / dependence 6 month prior, antipsychotic or benzodiazepines 7 days prior, P450 inhibition / induces 14 days prior, pregnant, breast feeding, risk of suicide</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 50-600 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56 days</p>	<p>Results: Anxiety: Insufficient data to calculate an effect size</p> <p>Depression: Change in HAM-D (% Remitted) at 8 weeks: Quetiapine vs Placebo - RR = 1.78 (0.53 , 5.97)</p> <p>Depression: Change in HAM-D (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 2.00 (0.76 , 5.26)</p> <p>Adverse Events: Quetiapine vs Placebo Anxiety: 0.0%(0/29) vs 10.3%(3/29) Constipation: 13.8%(4/29) vs 0.0%(0/29) Dizziness: 20.7%(6/29) vs 24.1%(7/29) Dry Mouth: 44.8%(13/29) vs 13.8%(4/29) Dysuria: 10.3%(3/29) vs 3.4%(1/29) Flu-Like Symptoms: 6.9%(2/29) vs 10.3%(3/29) Headache: 13.8%(4/29) vs 27.6%(8/29) Increased Appetite: 17.2%(5/29) vs 20.7%(6/29) Increased Dreaming/ Nightmares: 13.8%(4/29) vs 0.0%(0/29) Increased Weight (Based On Pt's Perception): 34.5%(10/29) vs 10.3%(3/29) Insomnia: 0.0%(0/29) vs 31.0%(9/29) Irritability/Restlessness: 13.8%(4/29) vs 17.2%(5/29) Nausea: 3.4%(1/29) vs 10.3%(3/29) Other AE: 41.4%(12/29) vs 41.4%(12/29) Pain: 10.3%(3/29) vs 13.8%(4/29) Sedation/ Somnolence/Lethargy: 86.2%(25/29) vs 48.3%(14/29)</p> <p>Withdrawals: Quetiapine vs Placebo Withdrawals:37.9%(11/29) vs 44.8%(13/29) Withdrawals Due To Adverse Events:27.6%(8/29) vs 6.9%(2/29) Withdrawals Due to Adverse Events: Increase Irritability:0.0%(0/29) vs 3.4%(1/29) Withdrawals Due to Adverse Events: Increased Appetite, Increased Irritability And Sedation/Somnolence/Lethargy:3.4%(1/29) vs 0.0%(0/29) Withdrawals Due to Adverse Events: Sedation/Somnolence/Lethargy:20.7%(6/29) vs 3.4%(1/29) Withdrawals Due to Adverse Events: Weight Gain And Fatigue:3.4%(1/29) vs 0.0%(0/29)</p>
<p>Keitner et al. 2009¹⁶⁵</p>	<p>Inclusion criteria: Depressed, failed current antidepressant trial.</p>	<p>Results: Depression: Change in HAM-D (% Remitted) at 4 weeks:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Depression</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Mean: 20</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 246 Eligible: 97 Entering: 97 Withdrawn: NR Lost to follow-up: NR Analyzed: 94</p> <p>Method of AE assessment: Monitored</p>	<p>MADRS \geq15, 18-65</p> <p>Exclusion criteria: Bipolar I or II, psychotic features, suicide risk, substance abuse / dependence, mod illness or seizures, ECT, pregnant or breast feeding, taking herbal meds</p> <p>Interventions: Placebo for 4 weeks vs Risperidone 0.5-3 mg/days flexible dose for 4 weeks</p> <p>Run-in/wash-out period: Run-in: Antidepressants for 5 week(s). Non-responder or partial responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28 days</p>	<p>Risperidone vs Placebo - RR = 1.95 (0.88 , 4.33)</p> <p>Depression: Change in HAM-D (% Responder) at 4 weeks: Risperidone vs Placebo - RR = 1.49 (0.83 , 2.68)</p> <p>Depression: Change in MADRS (% Remitted) at 4 weeks: Risperidone vs Placebo - RR = 2.13 (1.11 , 4.08)</p> <p>Depression: Change in MADRS (% Responder) at 4 weeks: Risperidone vs Placebo - RR = 1.65 (0.97 , 2.80)</p> <p>Adverse Events: Placebo vs Risperidone \geq7% Increase From Baseline Weight: 0.0%(0/33) vs 3.1%(2/64) Abdominal Gas: 6.1%(2/33) vs 0.0%(0/64) Any Adverse Events: 81.8%(27/33) vs 84.4%(54/64) Constipation: 9.1%(3/33) vs 12.5%(8/64) Dry Mouth: 3.0%(1/33) vs 14.1%(9/64) Fatigue: 6.1%(2/33) vs 0.0%(0/64) Headache: 15.2%(5/33) vs 9.4%(6/64) Increased Appetite: 0.0%(0/33) vs 15.6%(10/64) Insomnia: 9.1%(3/33) vs 3.1%(2/64) Tired: 6.1%(2/33) vs 0.0%(0/64) Weight Gain: 3.0%(1/33) vs 3.1%(2/64)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:21.2%(7/33) vs 15.6%(10/64)</p>
<p>Mahmoud et al. 2007¹⁶⁶</p> <p>Depression</p> <p>Risperidone</p> <p>Location: US</p>	<p>Inclusion criteria: 18-65, antidepressant monotherapy \geq 4 weeks, MDD, CGI-S \geq4</p> <p>Exclusion criteria: Pregnancy, suicide risk, serious illness, active substance or alcohol use disorders, current TCA (tricyclic antidepressant), MAO-I</p>	<p>Results: Depression: Change in HAM-D (% Remitted) at 6 weeks: Risperidone vs Placebo - RR = 2.29 (1.22 , 4.30)</p> <p>Depression: Change in HAM-D (% Responder) at 6 weeks: Risperidone vs Placebo - RR = 1.57 (1.10 , 2.23)</p> <p>Adverse Events:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Other-NOS</p> <p>Screened: 463 Eligible: 274 Entering: 274 Withdrawn: 33 Lost to follow-up: 9 Analyzed: 232</p> <p>Method of AE assessment: Elicited by investigator, reported spontaneously by patient</p>	<p>(monoamine oxidase inhibitor), mood stabilizer, antiepileptic, ADHD or narcolepsy medications</p> <p>Interventions: Placebo for 6 weeks vs Risperidone 0.25-2 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Run-in: Antidepressants for 4 week(s).</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42 days</p>	<p>Placebo vs Risperidone</p> <p>Any Treatment-Emergent Adverse Event: 54.1%(72/133) vs 44.7%(63/141)</p> <p>Arthralgia: 2.3%(3/133) vs 1.4%(2/141)</p> <p>Back Pain: 2.3%(3/133) vs 0.0%(0/141)</p> <p>Constipation: 2.3%(3/133) vs 3.5%(5/141)</p> <p>Death During The Study: 0.0%(0/133) vs 0.0%(0/141)</p> <p>Diarrhea: 3.8%(5/133) vs 2.1%(3/141)</p> <p>Disturbance In Attention: 0.0%(0/133) vs 2.1%(3/141)</p> <p>Dizziness: 2.3%(3/133) vs 3.5%(5/141)</p> <p>Dry Mouth: 0.8%(1/133) vs 5.0%(7/141)</p> <p>Dyspepsia: 3.0%(4/133) vs 2.1%(3/141)</p> <p>Fatigue: 0.0%(0/133) vs 3.5%(5/141)</p> <p>Headache: 14.3%(19/133) vs 8.5%(12/141)</p> <p>Hypertension: 2.3%(3/133) vs 0.0%(0/141)</p> <p>Insomnia: 1.5%(2/133) vs 4.3%(6/141)</p> <p>Lethargy: 2.3%(3/133) vs 0.7%(1/141)</p> <p>Nasopharyngitis: 3.0%(4/133) vs 2.1%(3/141)</p> <p>Nausea: 4.5%(6/133) vs 1.4%(2/141)</p> <p>Peripheral Edema: 0.8%(1/133) vs 2.8%(4/141)</p> <p>Sinusitis: 3.0%(4/133) vs 1.4%(2/141)</p> <p>Somnolence: 1.5%(2/133) vs 5.0%(7/141)</p> <p>Upper Respiratory Tract Infection: 2.3%(3/133) vs 0.0%(0/141)</p> <p>Weight Gain: 1.5%(2/133) vs 4.3%(6/141)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:12.0%(16/133) vs 18.4%(26/141) Withdrawals Due To Adverse Events:2.3%(3/133) vs 5.7%(8/141)</p>
<p>Bauer et al. 2009¹⁶²</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: Canada, Western Europe, Eastern Europe, Australia/New Zealand,</p>	<p>Inclusion criteria: 18-65 yrs old, diagnosed MDD, outpatients, HAM-D total score >= 20. HAM-D item I score >= 2, inadequate response during current episode to antidepressants.</p> <p>Exclusion criteria: Any DSM-IV Axis disorder other than MDD. DSM-IV Axis II disorder, duration of current MDD episode > 12 month or < 4 weeks from</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Quetiapine vs Placebo - RR = 1.42 (1.03 , 1.94)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Quetiapine vs Placebo - RR = 1.22 (1.01 , 1.48)</p> <p>Adverse Events: Placebo vs Quetiapine 150 mg/d vs Quetiapine 300 mg/d >=7% Increase In Body Weight At End of Treatment: 1.2%(2/163) vs 4.2%(7/167) vs</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>South Africa</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 572</p> <p>Eligible: NR</p> <p>Entering: 493</p> <p>Withdrawn: 66</p> <p>Lost to follow-up: 3</p> <p>Analyzed: 424</p> <p>Method of AE assessment: Monitored</p>	<p>enrollment, substance abuse, clinically significant medical illness, HAM-D item 3 score ≥ 3, require psychotherapy, received quetiapine $> 25\text{mg/day}$ for insomnia within 7 days before randomization, lack of quetiapine response.</p> <p>Interventions: Placebo for 6 weeks vs Quetiapine 50-150 mg/days fixed titration schedule for 6 weeks vs Quetiapine 50-300 mg/days fixed titration schedule for 6 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 14 day(s). Eligible patents were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42 days</p>	<p>4.3%(7/163)</p> <p>Clinically Relevant HDL Shifts To Elevated Values (≤ 40): 4.3%(7/163) vs 1.8%(3/167) vs 6.1%(10/163)</p> <p>Clinically Relevant LDL Shifts To Elevated Values (≥ 160): 11.0%(18/163) vs 16.2%(27/167) vs 12.3%(20/163)</p> <p>Clinically Relevant Prolactin Shifts To Elevated Values (Males ≥ 20, Females > 30): 1.8%(3/163) vs 1.2%(2/167) vs 2.5%(4/163)</p> <p>Clinically Relevant Shifts Glucose To Elevated Values (≥ 126): 2.5%(4/163) vs 2.4%(4/167) vs 6.7%(11/163)</p> <p>Clinically Relevant Shifts Tot Cholesterol To Elevated Values (≥ 240): 8.6%(14/163) vs 21.0%(35/167) vs 15.3%(25/163)</p> <p>Clinically Relevant Triglycerides Shifts To Elevated Values (≥ 200): 3.1%(5/163) vs 11.4%(19/167) vs 12.9%(21/163)</p> <p>Constipation: 3.7%(6/163) vs 4.2%(7/167) vs 10.4%(17/163)</p> <p>Dizziness: 7.4%(12/163) vs 11.4%(19/167) vs 9.2%(15/163)</p> <p>Dry Mouth: 6.7%(11/163) vs 20.4%(34/167) vs 35.6%(58/163)</p> <p>Fatigue: 3.1%(5/163) vs 13.2%(22/167) vs 14.7%(24/163)</p> <p>Headache: 9.8%(16/163) vs 9.0%(15/167) vs 8.0%(13/163)</p> <p>Nasopharyngitis: 6.1%(10/163) vs 3.0%(5/167) vs 3.1%(5/163)</p> <p>Nausea: 6.1%(10/163) vs 5.4%(9/167) vs 5.5%(9/163)</p> <p>Sedation: 4.3%(7/163) vs 9.6%(16/167) vs 12.9%(21/163)</p> <p>Somnolence: 3.1%(5/163) vs 16.8%(28/167) vs 23.3%(38/163)</p> <p>Withdrawals: Placebo vs Quetiapine 150 mg/d vs Quetiapine 300 mg/d Withdrawals: 11.0%(18/163) vs 12.6%(21/167) vs 18.4%(30/163) Withdrawals Due To Adverse Events: 3.1%(5/163) vs 6.6%(11/167) vs 11.7%(19/163)</p>
<p>Garakani et al. 2008¹⁶⁰</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: 18-65 years old, diagnosis of unipolar major depression without psychotic features, MADRS score > 15 at both screen and baseline</p> <p>Exclusion criteria: Received an antidepressant for the current episode or within 2 weeks of entering the study, a history of treatment -refractory</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 8 weeks: Quetiapine vs Placebo - RR = 0.87 (0.67 , 1.13)</p> <p>Adverse Events: Fluoxetine + placebo vs Fluoxetine+ quetiapine Anxiety: 12.3%(7/57) vs 7.0%(4/57) Dizziness And Lightheadedness: 12.3%(7/57) vs 17.5%(10/57) Dry Mouth: 8.8%(5/57) vs 12.3%(7/57) Fatigue: 7.0%(4/57) vs 8.8%(5/57)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 41</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 114</p> <p>Withdrawn: 29</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 87</p> <p>Method of AE assessment: Monitored</p>	<p>depression (failure to respond to adequate trials), primary diagnosis of any eating disorder / psychotic disorder / delirium / dementia / bipolar / OCD, any Axis II disorder that would interfere with the study, substance abuse, positive urine toxicology screen.</p> <p>Interventions: Placebo 25-100 mg/days flexible dose for 8 weeks vs Quetiapine 25-100 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Gastrointestinal Symptoms (Nausea, Diarrhea, And Constipation): 22.8%(13/57) vs 14.0%(8/57)</p> <p>Headache: 12.3%(7/57) vs 5.3%(3/57)</p> <p>Muscle And Joint Pain: 7.0%(4/57) vs 3.5%(2/57)</p> <p>Sedation: 7.0%(4/57) vs 26.3%(15/57)</p> <p>Withdrawals: Fluoxetine + placebo vs Fluoxetine+ quetiapine Withdrawals:19.3%(11/57) vs 28.1%(16/57)</p>
<p>Berman et al. 2009¹⁵⁶</p> <p>Depression</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p>	<p>Inclusion criteria: 18-65 years old, diagnosed major depressive episode >= 8weeks, inadequate response to previous antidepressants</p> <p>Exclusion criteria: Had received antidepressant with an adjunctive antipsychotic for > 3 weeks, psychosis, previously not tolerate any study antidepressants</p> <p>Interventions: Placebo for 6 weeks vs Aripiprazole 2-20 mg/days flexible dose for 6 weeks</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Aripiprazole vs Placebo - RR = 1.43 (0.96 , 2.12)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Aripiprazole vs Placebo - RR = 1.75 (1.30 , 2.35)</p> <p>Adverse Events: Aripiprazole Akathisia: Mild: 11.3%(20/177) Akathisia: Moderate: 5.1%(9/177) Akathisia: Severe: 1.7%(3/177) Aripiprazole vs Placebo Akathisia: Total: 18.1%(32/177) vs 3.5%(6/172) Clinically Significant Weight Gain (=7%) At Endpoint: 4.5%(8/177) vs 1.2%(2/172) Constipation: 5.6%(10/177) vs 3.5%(6/172) Diarrhea: 5.6%(10/177) vs 7.6%(13/172)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 3</p> <p>Age: Mean: 45</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Native American, Other-NOS</p> <p>Screened: 1147 Eligible: 349 Entering: 349 Withdrawn: 48 Lost to follow-up: 5 Analyzed: 296</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Run-in/wash-out period: Run-in: Antidepressants for 8 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	<p>Dizziness: 5.1%(9/177) vs 2.9%(5/172) Fatigue: 9.0%(16/177) vs 4.7%(8/172) Headache: 8.5%(15/177) vs 8.1%(14/172) Insomnia: 8.5%(15/177) vs 5.2%(9/172) Nausea: 4.0%(7/177) vs 5.8%(10/172) Restlessness: 12.4%(22/177) vs 3.5%(6/172) Serious AE: Arterial Occlusive Disease: 0.0%(0/177) vs 0.6%(1/172) Serious AE: Suicidal Ideation: 0.6%(1/177) vs 0.0%(0/172) Somnolence: 5.6%(10/177) vs 0.6%(1/172) Upper Respiratory Tract Infection: 7.3%(13/177) vs 7.6%(13/172) Vision Blurred: 7.3%(13/177) vs 1.7%(3/172)</p> <p>Withdrawals: Aripiprazole Withdrawal Due To Akathisia:1.1%(2/177) Aripiprazole vs Placebo Withdrawals:16.9%(30/177) vs 13.4%(23/172) Withdrawals Due To Adverse Events:6.2%(11/177) vs 1.7%(3/172)</p>
<p>Reeves et al. 2008¹⁶⁴</p> <p>Depression</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p>	<p>Inclusion criteria: 19 - 60, MDD and suicidal ideation despite treatment with up to 2 antidepressants for >= 3 weeks. MADRS >= 25, suicidal subscore >=4</p> <p>Exclusion criteria: Psychotic features, other major psychiatric diagnosis, pregnant or lactating</p> <p>Interventions: Placebo for 8 weeks vs Risperidone 0.5-2 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period:</p>	<p>Results: Depression: Change in MADRS (Total Score) at 8 weeks: Risperidone Augmentation vs Placebo Augmentation - WMD = -7.11 (-9.88 , -4.34)</p> <p>Adverse Events: Placebo vs Risperidone Bad Taste: 0.0%(0/12) vs 25.0%(3/12) Delayed Ejaculation: 25.0%(3/12) vs 0.0%(0/12) Diarrhea: 25.0%(3/12) vs 16.7%(2/12) Dizziness: 8.3%(1/12) vs 16.7%(2/12) Dry Mouth: 0.0%(0/12) vs 58.3%(7/12) Headache: 91.7%(11/12) vs 16.7%(2/12) Heartburn: 16.7%(2/12) vs 8.3%(1/12) Increased Appetite: 16.7%(2/12) vs 8.3%(1/12) Insomnia: 25.0%(3/12) vs 8.3%(1/12) Nausea: 25.0%(3/12) vs 16.7%(2/12) Somnolence: 8.3%(1/12) vs 16.7%(2/12)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 23 Withdrawn: 5 Lost to follow-up: NR Analyzed: 18</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 4, 7, 14, 21, 28, 42, 56 days</p>	<p>Withdrawals: Placebo vs Risperidone Withdrawals:41.7%(5/12) vs 8.3%(1/12)</p>
<p>Marcus et al. 2008¹⁵⁴</p> <p>Depression</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 44</p>	<p>Inclusion criteria: 18-65 years old, major depressive episode > = 8weeks, inadequate response to previous antidepressants</p> <p>Exclusion criteria: Previously reported Berman 2007</p> <p>Interventions: Placebo for 6 weeks vs Aripiprazole 2-20 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Run-in: Antidepressants for 8 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Aripiprazole vs Placebo - RR = 1.67 (1.10 , 2.54)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Aripiprazole vs Placebo - RR = 1.86 (1.28 , 2.72)</p> <p>Adverse Events: Aripiprazole vs Placebo Akathisia: 25.7%(49/191) vs 4.2%(8/190) At Least 1 AE: 80.6%(154/191) vs 63.2%(120/190) Clinically Significant Weight Gain (=7% From Double-Blind Baseline): 3.1%(6/191) vs 0.0%(0/190) Constipation: 5.2%(10/191) vs 2.6%(5/190) Deaths: 0.0%(0/191) vs 0.0%(0/190) Fatigue: 9.9%(19/191) vs 3.7%(7/190) Headache: 8.9%(17/191) vs 10.5%(20/190) Insomnia: 7.3%(14/191) vs 1.6%(3/190) Nausea: 5.2%(10/191) vs 4.2%(8/190) Restlessness: 9.4%(18/191) vs 0.5%(1/190) Serious AE: Cellulitis (Deemed Not Related To Study Medication): 0.5%(1/191) vs</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Native American, Other-NOS</p> <p>Screened: 1151 Eligible: 381 Entering: 382 Withdrawn: 57 Lost to follow-up: 0 Analyzed: 324</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	<p>0.0%(0/190) Somnolence: 6.8%(13/191) vs 3.7%(7/190) Suicide-Related AE During Double-Blind Randomized Phase: 0.0%(0/191) vs 0.0%(0/190) Tremor: 6.3%(12/191) vs 2.6%(5/190)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:15.2%(29/191) vs 14.7%(28/190) Withdrawals Due To Adverse Events:3.7%(7/191) vs 1.1%(2/190)</p>
<p>Dunner et al. 2007¹⁷⁶</p> <p>Depression</p> <p>Ziprasidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p>	<p>Inclusion criteria: 21-65, non response to at least 1 course of 4 weeks of antidepressants and MADRS \geq20</p> <p>Exclusion criteria: Psychotic disorder, PTSD, panic, OCD, substance abuse / dependence in past 3 month, history of treatment with atypical antipsychotic fluoxetine, MAO-1 or ECT 6 weeks prior, unstable medical illness, pregnant, breast feeding</p> <p>Interventions: Control Group vs Ziprasidone 40-80 mg/days flexible dose for 8 weeks vs Ziprasidone 80-160 mg/days flexible dose for duration not reported</p>	<p>Results: Depression: Change in MADRS at 8 weeks: Ziprasidone 80mg + Sertraline vs Sertraline - WMD = -1.53 (-2.73 , -0.34)</p> <p>Depression: Change in MADRS at 8 weeks: Ziprasidone 160mg + Sertraline vs Sertraline - WMD = -3.82 (-5.14 , -2.50)</p> <p>Adverse Events: Placebo vs Ziprasidone 160 mg vs Ziprasidone 80 mg Abnormal Thinking: 0.0%(0/21) vs 10.0%(2/20) vs 8.7%(2/23) Abnormal Vision: 0.0%(0/21) vs 20.0%(4/20) vs 4.3%(1/23) Agitation: 0.0%(0/21) vs 25.0%(5/20) vs 21.7%(5/23) Akathisia: 0.0%(0/21) vs 20.0%(4/20) vs 4.3%(1/23) Asthenia: 0.0%(0/21) vs 25.0%(5/20) vs 21.7%(5/23) At Least 1 Adverse Events: 38.1%(8/21) vs 80.0%(16/20) vs 95.7%(22/23) Constipation: 0.0%(0/21) vs 5.0%(1/20) vs 13.0%(3/23) Dizziness: 0.0%(0/21) vs 20.0%(4/20) vs 17.4%(4/23) Dry Mouth: 0.0%(0/21) vs 20.0%(4/20) vs 8.7%(2/23) Headache: 4.8%(1/21) vs 15.0%(3/20) vs 17.4%(4/23) Insomnia: 4.8%(1/21) vs 30.0%(6/20) vs 34.8%(8/23) Nausea: 0.0%(0/21) vs 20.0%(4/20) vs 4.3%(1/23)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 90 Eligible: 64 Entering: 64 Withdrawn: 29 Lost to follow-up: 0 Analyzed: 35</p> <p>Method of AE assessment: Monitored</p>	<p>Run-in/wash-out period: Run-in: Sertraline for 6 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 56 days</p>	<p>Required Dose Reduction Or Temporary Discontinuance Due To Adverse Events: 0.0%(0/21) vs 20.0%(4/20) vs 0.0%(0/23) Respiratory Infection: 0.0%(0/21) vs 5.0%(1/20) vs 17.4%(4/23) Somnolence: 9.5%(2/21) vs 15.0%(3/20) vs 21.7%(5/23) Tremor: 4.8%(1/21) vs 10.0%(2/20) vs 21.7%(5/23)</p> <p>Withdrawals: Placebo vs Ziprasidone 160 mg vs Ziprasidone 80 mg Withdrawals:28.6%(6/21) vs 55.0%(11/20) vs 52.2%(12/23) Withdrawals Due To Adverse Events:0.0%(0/21) vs 35.0%(7/20) vs 39.1%(9/23)</p>
<p>Berman et al. 2007¹⁵⁵</p> <p>Depression</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 4</p> <p>Age: Mean: 45</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Native American,</p>	<p>Inclusion criteria: Diagnosed major depressive episode >=8 weeks, inadequate response to antidepressant, (<50% reduction in depressive symptoms severity), HAM-D-17 >=18</p> <p>Exclusion criteria: Delirium, dementia, amnesic, cognitive disorder schizophrenia, bipolar disorders, OCD, PTSD, personality disorders, psychotic symptomatology, allergy, participated ARI trial within past month, drug abuse, received antipsychotic and antidepressant for >=3 weeks etc.</p> <p>Interventions: Placebo for 6 weeks vs Aripiprazole 2-20 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Run-in: Antidepressants for 8 week(s). Non-responders were randomized.</p> <p>Comorbidities:</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Aripiprazole vs Placebo - RR = 1.65 (1.08 , 2.53)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Aripiprazole vs Placebo - RR = 1.41 (1.01 , 1.98)</p> <p>Adverse Events: Aripiprazole vs Placebo >=7% Weight Gain: 7.1%(13/184) vs 1.1%(2/178) Akathisia: 22.8%(42/184) vs 4.5%(8/178) At Least One AE: 81.0%(149/184) vs 61.8%(110/178) Continuing Akathisia: 10.3%(19/184) vs 0.0%(0/178) Diarrhea: 3.3%(6/184) vs 5.6%(10/178) Dry Mouth: 3.3%(6/184) vs 6.2%(11/178) EPS-Related AEs: 27.2%(50/184) vs 9.6%(17/178) Fatigue: 6.0%(11/184) vs 3.4%(6/178) Headache: 6.0%(11/184) vs 10.7%(19/178) Insomnia: 7.6%(14/184) vs 2.2%(4/178) Nausea: 2.7%(5/184) vs 5.1%(9/178) Non-Akathisia EPS-Related AEs: 4.3%(8/184) vs 5.1%(9/178) Restlessness: 14.1%(26/184) vs 3.4%(6/178) Serious AE: Cellulitis And Staphylococcal Abscess: 0.0%(0/184) vs 0.6%(1/178) Serious AE: Contusion And Physical Assault: 0.0%(0/184) vs 0.6%(1/178) Serious AE: Exostosis: 0.0%(0/184) vs 0.6%(1/178) Serious AE: Pneumonia: 0.5%(1/184) vs 0.0%(0/178) Serious AE: Staphylococcal Cellulitis: 0.5%(1/184) vs 0.0%(0/178)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Eskimo/Inuit, Other-NOS</p> <p>Screened: 1044 Eligible: NR Entering: 362 Withdrawn: 31 Lost to follow-up: 7 Analyzed: 320</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	<p>Serious AEs: 1.1%(2/184) vs 1.7%(3/178) Suicidal Ideation: 0.0%(0/184) vs 1.1%(2/178) Upper Respiratory Tract Infection: 8.2%(15/184) vs 3.9%(7/178) Vision Blurred: 6.5%(12/184) vs 1.7%(3/178)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:13.0%(24/184) vs 10.1%(18/178) Withdrawals Due To Adverse Events:3.3%(6/184) vs 2.2%(4/178)</p>
<p>Zheng et al. 2007¹⁵⁷</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: Asia</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 1</p> <p>Age: Mean: 25</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p>	<p>Inclusion criteria: Diagnosed with MDD without psychotic symptoms, HAM-D score ≥ 18, BPRS item 4 score ≤ 4, item 11 score ≤ 3, had been treated unsuccessfully with ≥ 2 different types of antidepressants for ≥ 6 weeks</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Antidepressant 26.7-28 mg/days flexible dose for 4 weeks vs Quetiapine, Antidepressant 50-200 mg/days flexible dose for 4 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 56 days</p>	<p>Results: Depression: Change in HAM-D (% Remitted) at 4 weeks: Quetiapine vs Placebo - RR = 8.44 (1.17 , 60.94)</p> <p>Depression: Change in HAM-D (% Responder) at 4 weeks: Quetiapine vs Placebo - RR = 2.90 (1.13 , 7.47)</p> <p>Adverse Events: Quetiapine + antidepressants Somnolence: 25.0%(5/20) Quetiapine + antidepressants vs Antidepressants AEs: All Mild To Moderate In Intensity: 40.0%(8/20) vs 35.0%(7/20)</p> <p>Withdrawals: Quetiapine + antidepressants vs Antidepressants Withdrawals:10.0%(2/20) vs 5.0%(1/20) Withdrawals Due To Adverse Events:0.0%(0/20) vs 0.0%(0/20)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: 37</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>		
<p>Mattingly et al. 2006¹⁶¹</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 40 Withdrawn: 8 Lost to follow-up: 0</p>	<p>Inclusion criteria: Outpatients aged 18-65 years old, a primary diagnosis of major depression who were not psychotic, baseline HAM-D 17 \geq 20 following a \geq 6 weeks SSRI or SNRI treatment, HAM-D item I score \geq 2 had failed \geq 1 r-week trial of clinically appropriate dose of another antidepressant</p> <p>Exclusion criteria: Met DSM-IV criteria for substance abuse within 3 months, a history of clinically significant disease, had participated in a clinical trial in the past 90 days, had a known intolerance or lack of response to quetiapine, received mood stabilizers, other antipsychotics or antidepressants other than SSRIs or SNRIs \geq 2 weeks</p> <p>Interventions: Placebo 200-400 mg/days flexible dose for 8 weeks vs Quetiapine 200-400 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: SRI monotherapy for 8 week(s). Non-responders were randomized.</p>	<p>Results: Depression: Change in HAM-D (% Remitted) at 8 weeks: Quetiapine vs Placebo - RR = 2.83 (0.73 , 10.98)</p> <p>Depression: Change in HAM-D (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 2.12 (0.89 , 5.05)</p> <p>Adverse Events: Placebo vs Quetiapine Dry Mouth: 0.0%(0/14) vs 11.5%(3/26) Fatigue: 14.3%(2/14) vs 26.9%(7/26) Headache: 35.7%(5/14) vs 26.9%(7/26) Sedation/Insomnia: 7.1%(1/14) vs 7.7%(2/26)</p> <p>Withdrawals: Placebo vs Quetiapine Withdrawals:21.4%(3/14) vs 19.2%(5/26) Withdrawals Due To Adverse Events:14.3%(2/14) vs 0.0%(0/26)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Analyzed: 32</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56 days</p>	
<p>Gharabawi et al. 2006¹⁶⁷</p> <p>Depression</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 274 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Adult outpatients with DSM-IV MDD, had an incomplete response to \geq 8 weeks of antidepressant treatment</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo 0.25-2 mg/days average final dose for 6 weeks vs Risperidone 0.25-2 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 42 days</p>	<p>Results: Depression: Change in HAM-D (% Remitted) at 6 weeks: Risperidone vs Placebo - RR = 2.03 (1.10 , 3.75)</p> <p>Depression: Change in HAM-D (% Responder) at 6 weeks: Risperidone vs Placebo - RR = 1.44 (1.03 , 2.01)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Thase et al. 2007¹⁷⁴</p> <p>Depression</p> <p>Olanzapine</p> <p>Location: US, Canada</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 44</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 1313</p> <p>Eligible: 605</p> <p>Entering: 605</p> <p>Withdrawn: 146</p> <p>Lost to follow-up: 18</p> <p>Analyzed: 441</p> <p>Method of AE assessment: Not applicable</p>	<p>Inclusion criteria: Treatment resistant depression, 18-65 years old, HAM-D-17 \geq22</p> <p>Exclusion criteria: Current / post schizophrenia, other psychotic disorders, PTSD, pregnant or nursing females, post partum depression, MDD with atypical features, paranoid, schizoid, personality disorders, significant medical illness, concomitant medications with primary central nervous system activity except lorazepam with dose up to 4mg / week</p> <p>Interventions: Olanzapine, Naltrexone 6-18 mg/days flexible dose for 8 weeks vs Olanzapine 6-18 mg/days flexible dose for 8 weeks vs Naltrexone 50 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: Fluoxetine for 8 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Results: Depression: Change in MADRS at 8 weeks: Olanzapine+Fluoxetine vs Fluoxetine - WMD = -3.40 (-5.35 , -1.45)</p> <p>Depression: Change in MADRS at 8 weeks: Olanzapine+Fluoxetine vs Olanzapine - WMD = -3.70 (-5.60 , -1.80)</p> <p>Depression: Change in MADRS at 8 weeks: Olanzapine vs Fluoxetine - WMD = 0.30 (-1.52 , 2.12)</p> <p>Adverse Events: Fluoxetine vs Olanzapine vs Olanzapine/fluoxetine Deaths: 0.0%(0/206) vs 0.0%(0/199) vs 0.0%(0/200) Dry Mouth: 8.7%(18/206) vs 31.7%(63/199) vs 28.5%(57/200) Fatigue: 7.8%(16/206) vs 14.1%(28/199) vs 14.0%(28/200) Headache: 19.4%(40/206) vs 13.1%(26/199) vs 12.5%(25/200) Hypersomnia: 2.4%(5/206) vs 11.1%(22/199) vs 10.5%(21/200) Increase In Nonfasting Glucose From 140 To <200 mg/dL At Baseline To =200 mg/dL At Endpoint: 0.5%(1/206) vs 1.5%(3/199) vs 2.5%(5/200) Increase In Nonfasting Glucose From <140 mg/dL At Baseline To =200 mg/dL At Endpoint: 3.4%(7/206) vs 3.5%(7/199) vs 1.5%(3/200) Increase In Total Cholesterol From <200 mg/dL At Baseline To =240 mg/dL At Endpoint: 1.5%(3/206) vs 2.5%(5/199) vs 3.5%(7/200) Increase In Triglycerides From <150 mg/dL At Baseline To =500 mg/dL At Endpoint: 0.0%(0/206) vs 0.5%(1/199) vs 0.0%(0/200) Increased Appetite: 5.8%(12/206) vs 30.7%(61/199) vs 32.0%(64/200) Peripheral Edema: 1.0%(2/206) vs 7.5%(15/199) vs 12.0%(24/200) Serious AEs: Bipolar Disorder: 0.0%(0/206) vs 0.0%(0/199) vs 0.5%(1/200) Serious AEs: Pyrexia: 0.0%(0/206) vs 0.0%(0/199) vs 0.5%(1/200) Somnolence: 5.3%(11/206) vs 12.1%(24/199) vs 17.5%(35/200) Tremor: 8.7%(18/206) vs 8.0%(16/199) vs 10.5%(21/200) Weight Increased: 6.8%(14/206) vs 39.7%(79/199) vs 35.0%(70/200)</p> <p>Withdrawals: Fluoxetine vs Olanzapine vs Olanzapine/fluoxetine Withdrawals:19.4%(40/206) vs 36.2%(72/199) vs 26.0%(52/200) Withdrawals Due To Adverse Events:2.4%(5/206) vs 16.1%(32/199) vs 13.5%(27/200)</p>
<p>Nemeroff et al. 2004¹⁶³</p> <p>Depression</p>	<p>Inclusion criteria: Inpatients or outpatients aged 18-85 years old, DSM-IV diagnosis of MDD, 17-item HAM-D score \geq 20, failed to respond to 1-3</p>	<p>Results: Depression: Change in Proportion of patients that relapsed at 24 weeks: Risperidone + Citalopram vs Placebo +Citalopram - RR = 1.04 (0.82 , 1.31)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 241 Withdrawn: 23 Lost to follow-up: NR Analyzed: 218</p> <p>Method of AE assessment: Not reported</p>	<p>antidepressants other than citalopram or escitalopram given at least 6 weeks.</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 24 weeks vs Risperidone dosage not reported for 24 weeks</p> <p>Run-in/wash-out period: Run-in: Citalopram for 4-6 week(s). Non-responders were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 168 days</p>	
<p>Kim et al. 2007¹⁵³</p> <p>Depression</p> <p>Aripiprazole</p> <p>Location: Not reported</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: MDD, incomplete response to at least one historical treatment and one prospective treatment</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 6 weeks</p>	<p>Results: Depression: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Not applicable</p>	<p>vs Aripiprazole 2-20 mg/days frequency not reported for 6 weeks</p> <p>Run-in/wash-out period: Run-in: Antidepressants plus placebo for 8 week(s).</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 42 days</p>	
<p>El-Khalili et al. 2010¹⁵⁹</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: PEARL-D1448C00006</p> <p>Funding source: Industry</p> <p>Design: RCT only</p>	<p>Inclusion criteria: 18-65, MDD per DSM-IV, HAMD \geq20 - item I \geq 2, inadequate response to antidepressant</p> <p>Exclusion criteria: Axis I other than MDD within 6 month prior, significant Axis II, current MDD episode > 12 month or < 4 weeks, substance abuse or dependence 6 month prior, significant medical illness, suicide / homicide risk, HAMD item 3 \geq 3, suicide attempt 6 months prior, requiring starting psychotherapy</p> <p>Interventions: Placebo 998 Not reported/days fixed titration schedule for 6 weeks</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Quetiapine 150mg & 300mg vs Placebo - RR = 1.58 (1.15 , 2.19)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Quetiapine 150mg & 300mg vs Placebo - RR = 1.20 (0.98 , 1.47)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 659</p> <p>Eligible: NR</p> <p>Entering: 446</p> <p>Withdrawn: 77</p> <p>Lost to follow-up: 25</p> <p>Analyzed: 344</p> <p>Method of AE assessment: Monitored</p>	<p>vs</p> <p>Quetiapine 150 mg/days fixed titration schedule for 6 weeks</p> <p>vs</p> <p>Quetiapine 300 mg/days fixed titration schedule for 6 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for <=14 day(s). Patients who completed the wash-out period were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56 days</p>	
<p>Kordon et al. 2008¹⁹⁷</p> <p>OCD</p> <p>Quetiapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p>	<p>Inclusion criteria: Aged 18-65, diagnosis of OCD, Y-BOCS >= 18, treated with an SRI >= 12 weeks and non-responders (< 25% improvement in Y-BOCS)</p> <p>Exclusion criteria: Known intolerance or lack of response to quetiapine, a psychotic disorder, substance abuse, organic brain disease, epilepsy, known HIV infection, significant and unstable venal, cardiovascular, hepatic, hematologic, or endocrine conditions.</p> <p>Interventions: Placebo 100-600 mg/days flexible dose for 12 weeks</p> <p>vs</p> <p>Quetiapine 100-600 mg/days flexible dose for 12 weeks</p>	<p>Results: OCD: Change in YBOCS at 12 weeks: Quetiapine vs Placebo - RR = 2.11 (0.61 , 7.24)</p> <p>Adverse Events: Quetiapine vs Placebo</p> <p>Abdominal Pain Upper: 15.0%(3/20) vs 25.0%(5/20)</p> <p>Apathy: 15.0%(3/20) vs 10.0%(2/20)</p> <p>Constipation: 25.0%(5/20) vs 5.0%(1/20)</p> <p>Diarrhea: 5.0%(1/20) vs 25.0%(5/20)</p> <p>Disturbance In Attention: 25.0%(5/20) vs 5.0%(1/20)</p> <p>Dizziness: 15.0%(3/20) vs 5.0%(1/20)</p> <p>Dry Mouth: 50.0%(10/20) vs 15.0%(3/20)</p> <p>Dyspepsia: 35.0%(7/20) vs 5.0%(1/20)</p> <p>Fatigue: 85.0%(17/20) vs 65.0%(13/20)</p> <p>Headache: 35.0%(7/20) vs 55.0%(11/20)</p> <p>Hyperhidrosis: 30.0%(6/20) vs 50.0%(10/20)</p> <p>Increased Appetite: 15.0%(3/20) vs 15.0%(3/20)</p> <p>Influenza-Like Illness: 5.0%(1/20) vs 30.0%(6/20)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 40 Withdrawn: 10 Lost to follow-up: NR Analyzed: 30</p> <p>Method of AE assessment: Reported spontaneously by patient, observed</p>	<p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Personality Disorder</p> <p>Timing of outcome assessment: 14, 28, 42, 56, 70, 84 days</p>	<p>Nasopharyngitis: 5.0%(1/20) vs 20.0%(4/20) Nausea: 10.0%(2/20) vs 20.0%(4/20) Nightmare: 10.0%(2/20) vs 10.0%(2/20) SAE: Cramps In Lower Abdomen: 0.0%(0/20) vs 5.0%(1/20) SAE: Headache: 0.0%(0/20) vs 5.0%(1/20) SAE: Increased Cardiac Enzymes: 5.0%(1/20) vs 0.0%(0/20) SAE: Orthostatic Collapse: 0.0%(0/20) vs 5.0%(1/20) Subjects With At Least 1 AE: 95.0%(19/20) vs 100.0%(20/20) Subjects With At Least 1 Drug-Related AE: 95.0%(19/20) vs 55.0%(11/20) Subjects With At Least 1 Drug-Related SAE: 5.0%(1/20) vs 10.0%(2/20) Subjects With At Least 1 SAE: 5.0%(1/20) vs 15.0%(3/20) Vertigo: 45.0%(9/20) vs 25.0%(5/20)</p> <p>Withdrawals: Quetiapine vs Placebo Withdrawals:30.0%(6/20) vs 15.0%(3/20) Withdrawals Due To Adverse Events:20.0%(4/20) vs 5.0%(1/20)</p>
<p>Vulink et al.2009¹⁹⁹</p> <p>OCD</p> <p>Quetiapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: Mixed</p>	<p>Inclusion criteria: Age >= 18, OCD, YBOCS>=17 or 11 if only obsessions and compulsive were present</p> <p>Exclusion criteria: Use of antipsychotics or SRI's at effective dose for at least 8 weeks, MDD, or HAM-D 17>=17, pregnant or nursing, women not on contraception, organic mental disorder, epilepsy, central nervous system disorder or stroke within last year, bipolar, schizophrenia or other psychotic disorders, subrelated disorder within 6 months, personality disorder, tics or Tourette's, any clinically significant acute or unstable medical condition, allergy to quetiapine, behavioral or cognitive therapy 3 month prior, suicide risk</p> <p>Interventions: Placebo for 10 weeks vs Quetiapine 50-450 mg/days fixed titration schedule for 10 weeks</p>	<p>Results: OCD: Change in YBOCS (Total Score) at 10 weeks: Quetiapine vs Placebo - WMD = -3.80 (-6.72 , -0.88)</p> <p>Adverse Events: Placebo vs Quetiapine Concentration Problems: 10.8%(4/37) vs 7.7%(3/39) Dizziness: 10.8%(4/37) vs 23.1%(9/39) Dry Mouth: 13.5%(5/37) vs 33.3%(13/39) Headache: 35.1%(13/37) vs 25.6%(10/39) Increased Appetite: 10.8%(4/37) vs 17.9%(7/39) Muscular Pain: 16.2%(6/37) vs 5.1%(2/39) Nausea: 37.8%(14/37) vs 5.1%(2/39) Palpitations: 10.8%(4/37) vs 7.7%(3/39) Sexual Problems: 43.2%(16/37) vs 41.0%(16/39) Sleeplessness: 29.7%(11/37) vs 0.0%(0/39) Somnolence: 56.8%(21/37) vs 84.6%(33/39) Sweating: 27.0%(10/37) vs 12.8%(5/39) Tremor: 27.0%(10/37) vs 15.4%(6/39) Weight Gain: 21.6%(8/37) vs 53.8%(21/39)</p> <p>Withdrawals: Placebo vs Quetiapine</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Not reported</p> <p>Screened: 249 Eligible: 143 Entering: 76 Withdrawn: 0 Lost to follow-up: 0 Analyzed: 66</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression</p> <p>Timing of outcome assessment: 14, 21, 28, 42, 56, 70 days</p>	<p>Withdrawals:5.4%(2/37) vs 20.5%(8/39) Quetiapine Withdrawals Due To Adverse Events:17.9%(7/39)</p>
<p>Denys et al. 2006²⁰¹ OCD Quetiapine Location: Not reported Trial: Not reported Funding source: Industry Design: RCT only Setting: Not reported Jadad: 2 Age: Not reported Sex: Race: Not reported Screened: NR</p>	<p>Inclusion criteria: Patients with primary OCD according to DSM-IV criteria</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Control Group vs Quetiapine dosage not reported for 10 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 70 days</p>	<p>Results: OCD: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Eligible: NR Entering: NR Withdrawn: 9 Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Not reported</p>		
<p>Ozdemir et al.²⁴⁰</p> <p>PTSD</p> <p>Quetiapine</p> <p>Location: Turkey</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 94 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p>	<p>Inclusion criteria: 18-55 years old, DSM-IV diagnosis of PTSD</p> <p>Exclusion criteria: Comorbid psychotic disorder, substance abuse, treated with SSRI previous 2 weeks, severe illness, abnormal lab test results, pregnant</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 166 (25-750) mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 56 days</p>	<p>Results: PTSD: Change in CAPS (ITT Results) at 8 weeks: Quetiapine + SSRI vs Placebo + SSRI - WMD = -3.60 (-16.83 , 9.63)</p> <p>PTSD: Change in CAPS (Per Protocol Results) at 8 weeks: Quetiapine + SSRI vs Placebo + SSRI - WMD = -17.00 (-27.80 , -6.20)</p> <p>Adverse Events: Placebo + Sertraline vs Quetiapine + sertraline At Least 1 Ae: 66.0%(31/47) vs 59.6%(28/47) Dizziness: 17.0%(8/47) vs 4.3%(2/47) Drowsiness: 6.4%(3/47) vs 17.0%(8/47) Dry Mouth: 2.1%(1/47) vs 17.0%(8/47) Insomnia: 17.0%(8/47) vs 2.1%(1/47) Mild Aes: 25.5%(12/47) vs 31.9%(15/47) Moderate Aes: 44.7%(21/47) vs 48.9%(23/47) Nausea: 12.8%(6/47) vs 10.6%(5/47) Somnolence: 4.3%(2/47) vs 8.5%(4/47) Vertigo: 8.5%(4/47) vs 2.1%(1/47)</p> <p>Withdrawals: Placebo + Sertraline vs Quetiapine + sertraline Withdrawals Due To Adverse Events:21.3%(10/47) vs 17.0%(8/47)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Monitored		
<p>Grabowski et al. 2004²⁷⁴</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: 120 Eligible: NR Entering: 96 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-50, dual dependent (cocaine and heroin) good medical health, without other psych diagnosis (except nicotine dependence)</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 26 weeks vs Risperidone 2 mg/days frequency not reported for 26 weeks vs Risperidone 4 mg/days frequency not reported for 26 weeks</p> <p>Run-in/wash-out period: Wash-out: Risperidone stabilization for 2 weeks. Patients in symptomatic remission were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Placebo vs Risperidone 2mg vs Risperidone 4mg Withdrawals:78.8%(26/33) vs 65.6%(21/32) vs 54.8%(17/31)</p>
<p>Guardia et al. 2011²⁶⁰</p> <p>Substance abuse</p>	<p>Inclusion criteria: 18-65, outpatient, alcohol dependence per DSM-IV</p>	<p>Results: Substance Abuse: Change in Abstinent Days - Self Report at 12 weeks: Quetiapine + Naltrexone vs Placebo + Naltrexone - WMD = -1.30 (-4.82 , 2.22)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Quetiapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 62</p> <p>Withdrawn: 15</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 47</p> <p>Method of AE assessment: Monitored</p>	<p>Exclusion criteria: Pregnant, nursing, woman without contraception, severe medical or psychiatric disorders, renal failure or hepatic impairment, operates public transport vehicle or hazardous machinery, leukopenia, contraindication to study drug.</p> <p>Interventions: Placebo 172.5 mg/days flexible dose for 12 weeks vs Quetiapine 127.5 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Run-in: Naltrexone + placebo for 1 week(s). Patients who met the study criteria were randomized.</p> <p>Comorbidities: Anxiety, Depression</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 56, 84, 112 days</p>	<p>Adverse Events: Naltrexone + Placebo vs Naltrexone + Quetiapine Anxiety: 3.1%(1/32) vs 6.7%(2/30) Asthenia/Lassitude: 3.1%(1/32) vs 0.0%(0/30) Constipation: 0.0%(0/32) vs 3.3%(1/30) Decreased Libido: 0.0%(0/32) vs 3.3%(1/30) Dizziness: 3.1%(1/32) vs 0.0%(0/30) Dry Mouth: 3.1%(1/32) vs 6.7%(2/30) Dyspepsia: 3.1%(1/32) vs 0.0%(0/30) Sae: Tonsillitis Unrelated To Study Medication: 0.0%(0/32) vs 3.3%(1/30) Somnolence: 3.1%(1/32) vs 6.7%(2/30) Tension/Inner Unrest: 6.3%(2/32) vs 3.3%(1/30)</p> <p>Withdrawals: Naltrexone + Placebo vs Naltrexone + Quetiapine Withdrawals:12.5%(4/32) vs 36.7%(11/30) Withdrawals Due To Adverse Events:3.1%(1/32) vs 6.7%(2/30)</p>

AE=Adverse Event, NR=Not Reported

Quality

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Zeni et al. 2009 ⁸⁰ ADHD Aripiprazole	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Not described</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Don't know</p> <p>Was the care provider masked? Don't know</p> <p>Were patients masked? Don't know</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Khan et al. ⁹¹ Anxiety Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Don't know</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
McIntyre et al. 2007 ⁸⁶ Anxiety, Depression Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Keitner et al. 2009 ¹⁶⁵ Depression Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Mahmoud et al. 2007 ¹⁶⁶ Depression Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Yes</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Bauer et al. 2009 ¹⁶² Depression Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Garakani et al. 2008 ¹⁶⁰ Depression Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Berman et al. 2009 ¹⁵⁶ Depression Aripiprazole	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Reeves et al. 2008 ¹⁶⁴ Depression Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Marcus et al. 2008 ¹⁵⁴ Depression Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Dunner et al. 2007 ¹⁷⁶ Depression Ziprasidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Open</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? No</p> <p>Were patients masked? No</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Berman et al. 2007 ¹⁵⁵ Depression Aripiprazole	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Zheng et al. 2007 ¹⁵⁷ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Mattingly et al. 2006 ¹⁶¹ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Gharabawi et al. 2006 ¹⁶⁷ Depression Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Thase et al. 2007 ¹⁷⁴ Depression Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Nemeroff et al. 2004 ¹⁶³ Depression Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Kim et al. 2007 ¹⁵³ Depression Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
<p>El-Khalili et al. 2010¹⁵⁹</p> <p>Depression</p> <p>Quetiapine</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
<p>Kordon et al. 2008¹⁹⁷</p> <p>OCD</p> <p>Quetiapine</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Vulink et al. 2009 ¹⁹⁹ OCD Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Denys et al. 2006 ²⁰¹ OCD Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Ozdemir et al. ²⁴⁰ PTSD Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Grabowski et al. 2004 ²⁷⁴ Substance abuse Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Guardia et al. 2011 ²⁶⁰ Substance abuse Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

AE=Adverse Event, NR=Not Reported

Placebo-Controlled Trials

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Armenteros et al. 2007⁷⁷</p> <p>ADHD</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 25 Withdrawn: 2 Lost to follow-up: 0 Analyzed: 23</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: ADHD, treated constant doses of stimulant for 3 weeks prior, aggressive behavior, AQPA of ≤ 0, CGI-S ≥ 4, IQ ≥ 75, normal physical and labs</p> <p>Exclusion criteria: Substance use disorder, unstable illness, history of intolerance or failure to respond to risperidone, suicidal or homicidal</p> <p>Interventions: Placebo for 28 days vs Risperidone 0.5-2 mg/days flexible dose for 28 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety</p> <p>Timing of outcome assessment: 7, 14, 21, 28 days</p>	<p>Results: ADHD: Change in CAS-P (improvement = $\geq 30\%$) at 4 weeks: Risperidone vs Placebo - RR = 1.19 (0.89 , 1.59)</p> <p>Adverse Events: Placebo vs Risperidone Abdominal Pain: 7.7%(1/13) vs 25.0%(3/12) Agitation: 0.0%(0/13) vs 8.3%(1/12) At Least One Adverse Event: 76.9%(10/13) vs 58.3%(7/12) Increased Appetite: 0.0%(0/13) vs 8.3%(1/12) Somnolence: 15.4%(2/13) vs 8.3%(1/12) Vomiting: 23.1%(3/13) vs 16.7%(2/12)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals: 7.7%(1/13) vs 8.3%(1/12) Withdrawals Due To Adverse Events: 0.0%(0/13) vs 0.0%(0/12)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Tramontina et al. 2009⁷⁹</p> <p>ADHD</p> <p>Aripiprazole</p> <p>Location: Latin America</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 5</p> <p>Age: Mean: 12</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 710 Eligible: 43 Entering: 43 Withdrawn: 2 Lost to follow-up: 0 Analyzed: 41</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Inclusion criteria: Age 8-17, bipolar I or II disorder comorbid ADHD acutely manic or mixed state, clear reports of ADHD symptom onset preceding any mood symptomatology</p> <p>Exclusion criteria: Estimated IQ < 70, use of any medication 4 weeks prior to entering the study, pervasive developmental disorder, schizophrenia, substance abuse, suicide risk, previous use of aripiprazole, pregnancy, chronic diseases</p> <p>Interventions: Placebo 2-20 mg/days flexible dose for 6 weeks vs Aripiprazole 2-20 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	<p>Results: ADHD: Change in SNAP-IV Total Score (Total Score) at 6 weeks: Aripiprazole vs Placebo - WMD = 0.05 (-0.34 , 0.44)</p> <p>Adverse Events: Excluded from analysis: Reflexes Change: 5.6%(1/18) vs 0.0%(0/25) Rhinitis: 27.8%(5/18) vs 64.0%(16/25) Sialorrhea: 72.2%(13/18) vs 52.0%(13/25) Skin Rash: 0.0%(0/18) vs 4.0%(1/25) Slowness Of Thought: 5.6%(1/18) vs 12.0%(3/25) Somnolence: 94.4%(17/18) vs 76.0%(19/25) Suicidal Ideation: 27.8%(5/18) vs 20.0%(5/25) Sweating: 55.6%(10/18) vs 44.0%(11/25) Tiredness: 83.3%(15/18) vs 56.0%(14/25) Tremors: 44.4%(8/18) vs 32.0%(8/25) Vomiting: 27.8%(5/18) vs 20.0%(5/25)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:5.6%(1/18) vs 4.0%(1/25) Withdrawals Due To Adverse Events:5.6%(1/18) vs 0.0%(0/25)</p>
<p>Bandelow et al. 2009⁸⁸</p> <p>Anxiety</p>	<p>Inclusion criteria: 18-65 years old, diagnosed GAD, HAM-A total score >= 20 with item 1 and 2 scores >=</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 1.36 (1.17 , 1.59)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Quetiapine</p> <p>Location: Canada, Western Europe, Eastern Europe, Latin America, South Africa</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 1054 Eligible: NR Entering: 873 Withdrawn: 188 Lost to follow-up: 9 Analyzed: 473</p> <p>Method of AE assessment: Monitored</p>	<p>2, MADRS total score <= 16, CGI-S score >=4 at enrollment and randomization.</p> <p>Exclusion criteria: Diagnosis of any DSM-IV-TR Axis I disorder other than GAD within 6 months or DSM -IV-TR Axis II disorder, MADRS item 10 score >=4, suicide attempt, alcohol abuse</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 50-150 mg/days fixed titration schedule for 8 weeks vs Quetiapine 50 mg/days fixed single dose for 8 weeks vs Paroxetine 20 mg/days fixed single dose for 8 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 1-4 week(s). Eligible patents were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 1, 4, 7, 14, 21, 28, 42, 56 days</p>	<p>Adverse Events: Paroxetine vs Placebo vs Quetiapine 150 mg vs Quetiapine 50mg >=7% Increase In Body Weight At End of Treatment: 4.6%(10/217) vs 2.3%(5/217) vs 6.9%(15/218) vs 4.5%(10/221) Anxiety: 5.1%(11/217) vs 0.5%(1/217) vs 1.4%(3/218) vs 1.4%(3/221) Constipation: 2.8%(6/217) vs 1.4%(3/217) vs 6.0%(13/218) vs 4.5%(10/221) Diarrhea: 5.5%(12/217) vs 4.6%(10/217) vs 3.7%(8/218) vs 3.2%(7/221) Dizziness: 13.4%(29/217) vs 6.0%(13/217) vs 15.6%(34/218) vs 11.8%(26/221) Dry Mouth: 9.7%(21/217) vs 6.0%(13/217) vs 25.7%(56/218) vs 15.8%(35/221) Extrapyramidal Adverse Events: 8.3%(18/217) vs 1.8%(4/217) vs 5.0%(11/218) vs 6.8%(15/221) Fasting HDL Cholesterol =40 mg/dL At End of Treatment: 1.4%(3/217) vs 5.5%(12/217) vs 3.7%(8/218) vs 2.7%(6/221) Fasting Total Cholesterol =240 mg/dL At End of Treatment: 6.5%(14/217) vs 3.2%(7/217) vs 5.0%(11/218) vs 4.1%(9/221) Fasting Triglycerides >=200 mg/dL At End of Treatment: 3.7%(8/217) vs 2.8%(6/217) vs 8.3%(18/218) vs 3.2%(7/221) Fatigue: 9.2%(20/217) vs 3.7%(8/217) vs 16.5%(36/218) vs 14.9%(33/221) Headache: 17.1%(37/217) vs 18.0%(39/217) vs 12.4%(27/218) vs 16.3%(36/221) Insomnia: 13.4%(29/217) vs 6.5%(14/217) vs 8.7%(19/218) vs 7.7%(17/221) Nasopharyngitis: 6.0%(13/217) vs 3.7%(8/217) vs 2.3%(5/218) vs 3.2%(7/221) Nausea: 24.4%(53/217) vs 9.2%(20/217) vs 11.9%(26/218) vs 11.3%(25/221) Overall Incidence Of Adverse Events: 72.8%(158/217) vs 55.8%(121/217) vs 76.1%(166/218) vs 71.0%(157/221) Sedation: 2.3%(5/217) vs 0.5%(1/217) vs 8.3%(18/218) vs 6.3%(14/221) Sexual Dysfunction: 7.4%(16/217) vs 2.3%(5/217) vs 1.8%(4/218) vs 0.9%(2/221) Somnolence: 11.1%(24/217) vs 4.6%(10/217) vs 25.2%(55/218) vs 21.7%(48/221) Treatment-Related Adverse Events: 58.5%(127/217) vs 34.6%(75/217) vs 65.6%(143/218) vs 58.8%(130/221) Paroxetine vs Placebo vs Quetiapine 50mg Fasting LDL Cholesterol = 160 mg/dL At End of Treatment: 6.5%(14/217) vs 3.7%(8/217) vs 3.2%(7/221) Quetiapine 150 mg Fasting LDL Cholesterol = >160 mg/dL At End of Treatment: 4.1%(9/218) Quetiapine 50mg vs Quetiapine 150 mg vs Placebo vs Paroxetine Fasting Glucose =>126 mg/dL At End of Treatment: 0.9%(2/221) vs 0.5%(1/218) vs 1.4%(3/217) vs 1.4%(3/217)</p> <p>Withdrawals: Paroxetine vs Placebo vs Quetiapine 150 mg vs Quetiapine 50mg Withdrawals:45.2%(98/217) vs 41.9%(91/217) vs 48.2%(105/218) vs 48.0%(106/221)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
		Withdrawals Due To Adverse Events:7.8%(17/217) vs 4.1%(9/217) vs 16.1%(35/218) vs 11.8%(26/221)
<p>Barnett et al. 2002⁸³</p> <p>Anxiety</p> <p>Olanzapine</p> <p>Location: Not reported</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Mean: 18</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 12</p> <p>Entering: 12</p> <p>Withdrawn: 2</p> <p>Lost to follow-up: 3</p> <p>Analyzed: 7</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-65, social anxiety disorder, DSM-IV of social phobia of, brief social phobia scale (BSPS) >= 20</p> <p>Exclusion criteria: NR</p> <p>Interventions: Placebo 5 mg/days flexible dose for 8 weeks vs Olanzapine 5-20 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: Placebo for 1 week(s).</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 21, 28, 42, 56 days</p>	<p>Results: Anxiety: Change in Brief Social Phobia Scale at 8 weeks: Olanzapine vs Placebo - WMD = -10.60 (-26.09 , 4.89)</p> <p>Adverse Events: Olanzapine vs Placebo Constipation: 14.3%(1/7) vs 0.0%(0/5) Drowsiness: 57.1%(4/7) vs 0.0%(0/5) Dry Mouth: 42.9%(3/7) vs 0.0%(0/5) Headache: 0.0%(0/7) vs 20.0%(1/5) Significant Changes On The BAS Or AIMS: 0.0%(0/7) vs 0.0%(0/5) Thirst: 14.3%(1/7) vs 0.0%(0/5) Weight Gain: 0.0%(0/7) vs 20.0%(1/5)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:42.9%(3/7) vs 40.0%(2/5) Withdrawals Due To Adverse Events:14.3%(1/7) vs 20.0%(1/5)</p>
<p>Brawman-Mintzer et al. 2005⁹⁸</p> <p>Anxiety</p>	<p>Inclusion criteria: Age >=18, GAD, HAM-A >=18, CGI-S >=4, Covi > Raskin score despite adequate treatment >= 4 weeks</p>	<p>Results: Anxiety: Change in HAM-A (Total Score) at 5 weeks: Risperidone vs Placebo - WMD = -3.60 (-6.88 , -0.32)</p> <p>Adverse Events:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 80-99% Female</p> <p>Race: Caucasian</p> <p>Screened: NR Eligible: NR Entering: 40 Withdrawn: NR Lost to follow-up: NR Analyzed: 31</p> <p>Method of AE assessment: Monitored</p>	<p>Exclusion criteria: MDD 1 month prior, substance use disorder 6 month prior, bipolar or psychotic disorder</p> <p>Interventions: Placebo for 5 weeks vs Risperidone 0.5-1.5 mg/days flexible dose for 5 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35 days</p>	<p>Placebo vs Risperidone Blurred Vision: 0.0%(0/20) vs 15.0%(3/20) Dizziness: 15.0%(3/20) vs 20.0%(4/20) Required Adjunctive Treatment With Anticholinergic Agents: 0.0%(0/20) vs 0.0%(0/20) Somnolence: 15.0%(3/20) vs 45.0%(9/20)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:20.0%(4/20) vs 25.0%(5/20) Withdrawals Due To Adverse Events:5.0%(1/20) vs 15.0%(3/20)</p>
<p>Donahue et al. 2009⁹⁵</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source:</p>	<p>Inclusion criteria: Diagnosis of SAD and clinically significant public speaking</p> <p>Exclusion criteria: Current contraindications or a history of sensitivity to quetiapine, current regular use of benzodiazepine, tranquilizer or antipsychotic medications, active psychotic/manic/depressed episode, unstable diabetes mellitus, heart disease, neurologic</p>	<p>Results: Anxiety: Cross over study</p> <p>Adverse Events: Excluded from analysis: Sample size by group not reported</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 81 Eligible: 44 Entering: 24 Withdrawn: 3 Lost to follow-up: 1 Analyzed: NR</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>disorder, liver disease</p> <p>Interventions: Placebo for 1 hours vs Quetiapine 25 mg/days fixed single dose for 1 hours</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 1, 2, 3, 4 minutes</p>	
<p>Hirschfeld et al. 2006⁹²</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p>	<p>Inclusion criteria: Outpatients aged 18-65. bipolar I or II disorder, current episode depressed, with a duration between 4 weeks and 1 year, HAM-D score ≥ 2, young mania rating scale score ≤ 12.</p> <p>Exclusion criteria: Diagnosed Axis I disorder other than bipolar disorder within 6 months, history of nonresponse to adequate trial during current episode, substance abuse within 12 months.</p> <p>Interventions: Placebo for 8 weeks vs</p>	<p>Results: Anxiety: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 3</p> <p>Age: Mean: 37</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 838</p> <p>Eligible: 542</p> <p>Entering: 542</p> <p>Withdrawn: 216</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 326</p> <p>Method of AE assessment: Not reported</p>	<p>Quetiapine 50-300 mg/days frequency not reported for 8 weeks</p> <p>vs</p> <p>Quetiapine 50-600 mg/days frequency not reported for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	
<p>Pandina et al. 2007⁹⁹</p> <p>Anxiety</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Not reported</p> <p>Sex: Mixed</p>	<p>Inclusion criteria: 15-65, GAD, CGI-S ≥ 4, antidepressant, benzodiazepine, buspirone or a combination of an antidepressants plus benzodiazepine or buspirone for at least 8 weeks prior and stable x 4 weeks</p> <p>Exclusion criteria: Pregnancy, suicide risk, serious illness, active substance abuse disorder, history of clozapine, other agents to manage anxiety, other axis I</p> <p>Interventions: Placebo 0.25-2 mg/days flexible dose for 4 weeks</p> <p>vs</p> <p>Risperidone 0.25-2 mg/days flexible dose for 4 weeks</p> <p>Run-in/wash-out period: Not reported</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 6 weeks: Risperidone vs Placebo - RR = 0.99 (0.78 , 1.25)</p> <p>Withdrawals: Placebo augmentation vs Risperidone augmentation Withdrawals:21.1%(41/194) vs 23.5%(46/196) Withdrawals Due To Adverse Events:5.2%(10/194) vs 10.7%(21/196)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Caucasian, African Ancestry, Hispanic, Other-NOS</p> <p>Screened: 453 Eligible: 417 Entering: 417 Withdrawn: 76 Lost to follow-up: 11 Analyzed: 303</p> <p>Method of AE assessment: Monitored</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	
<p>Pollack et al. 2006⁸⁴</p> <p>Anxiety</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 46 Eligible: 24</p>	<p>Inclusion criteria: 18-72 DSM-IV generalized anxiety disorder comorbid depression on dysthymia and other anxiety disorders except for PTSD and OCD if GAD was considered primary by the clinician and patient based on disorder severity and associated distress.</p> <p>Exclusion criteria: Bipolar or psychotic disorders, alcohol or substance abuse or dependence within the last 6 months or those receiving concurrent structured psychotherapies directed at the GAD.</p> <p>Interventions: Placebo for 6 weeks vs Olanzapine 2.5-20 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Run-in: Fluoxetine for 6 week(s). Symptomatic patients were randomized.</p> <p>Comorbidities: Depression</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 6 weeks: Olanzapine vs Placebo - RR = 6.67 (0.93 , 47.59)</p> <p>Adverse Events: Olanzapine vs Placebo At Least One AE: 100.0%(12/12) vs 100.0%(12/12) Gained =7% Of Their Body Weight: 16.7%(2/12) vs 0.0%(0/12) Gastrointestinal Distress: 33.3%(4/12) vs 25.0%(3/12) Increased Appetite: 25.0%(3/12) vs 16.7%(2/12) Sedation: 91.7%(11/12) vs 41.7%(5/12) Sexual Dysfunction: 16.7%(2/12) vs 25.0%(3/12) Weight Gain: 58.3%(7/12) vs 16.7%(2/12)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:41.7%(5/12) vs 16.7%(2/12) Withdrawals Due To Adverse Events:33.3%(4/12) vs 8.3%(1/12) Withdrawals Due to Adverse Events: Sedation:33.3%(4/12) vs 8.3%(1/12)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Entering: 24 Withdrawn: NR Lost to follow-up: NR Analyzed: 17</p> <p>Method of AE assessment: Monitored</p>	<p>Timing of outcome assessment: 42, 84 days</p>	
<p>Simon et al. 2008⁸⁵</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry</p> <p>Screened: 101 Eligible: 24 Entering: 22 Withdrawn: 6 Lost to follow-up: NR Analyzed: 16</p> <p>Method of AE</p>	<p>Inclusion criteria: Did not receive remission of GAD in >=18</p> <p>Exclusion criteria: <= 7 HAM-A, pregnant / lactating, MD, dysthymia, panic, social phobia, bipolar, psychotic, PTSD, OCD, alcohol or substance abuse / dependence 6 month prior, unstable illness</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 25-400 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: SRI monotherapy for 10 week(s). Non-responders were randomized.</p> <p>Comorbidities: Anxiety, Depression</p> <p>Timing of outcome assessment: 56 days</p>	<p>Results: Anxiety: Change in HAM-A (Total Score) at 8 weeks: Quetiapine vs Placebo - WMD = -2.36 (-7.99 , 3.27)</p> <p>Adverse Events: Placebo+Paroxetine vs Placebo+Paroxetine vs Quetiapine+Paroxetine vs Quetiapine+Paroxetine Diarrhea: 0.0%(0/11) vs 18.2%(2/11) vs 27.3%(3/11) vs 0.0%(0/11) Placebo+Paroxetine vs Quetiapine+Paroxetine Constipation: 18.2%(2/11) vs 0.0%(0/11) Dry Mouth: 0.0%(0/11) vs 27.3%(3/11) Insomnia: 27.3%(3/11) vs 0.0%(0/11) Nausea: 0.0%(0/11) vs 18.2%(2/11) Sedation: 0.0%(0/11) vs 54.5%(6/11) Sexual Dysfunction: 18.2%(2/11) vs 18.2%(2/11) Vivid Dreams: 27.3%(3/11) vs 0.0%(0/11) Weight Gain: 18.2%(2/11) vs 0.0%(0/11)</p> <p>Withdrawals: Placebo+Paroxetine vs Quetiapine+Paroxetine Withdrawals:9.1%(1/11) vs 45.5%(5/11) Withdrawals Due To Adverse Events:9.1%(1/11) vs 36.4%(4/11)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
assessment: Monitored, elicited by investigator		
<p>Vaishnavi et al. 2007⁸⁹</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 15 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-65, outpatients, social anxiety disorder, CGI-S\geq4, -BSPS\geq20, negative pregnancy test</p> <p>Exclusion criteria: Bipolar, schizophrenia or other psychotic disorder, mental retardation, pervasive developmental disorder, cognitive disorder due to general medical condition, other anxiety disorder, MDD, history of substance dependence 6 month prior, suicide risk, medical illness, psychotropic medication and history of hypersensitivity to quetiapine</p> <p>Interventions: Placebo 50-400 mg/days flexible dose for 8 weeks vs Quetiapine 50-400 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 21, 35, 56 days</p>	<p>Results: Anxiety: Change in BSPS at 8 weeks: Quetiapine vs Placebo - WMD = 30.50 (16.86 , 44.14)</p> <p>Adverse Events: Quetiapine vs Placebo Blurred Vision: 10.0%(1/10) vs 0.0%(0/5) Dizziness: 30.0%(3/10) vs 0.0%(0/5) Drowsiness: 50.0%(5/10) vs 0.0%(0/5) Headache: 10.0%(1/10) vs 0.0%(0/5) Nausea: 20.0%(2/10) vs 0.0%(0/5) Sweating: 10.0%(1/10) vs 0.0%(0/5) Swelling: 10.0%(1/10) vs 0.0%(0/5) Thirst: 10.0%(1/10) vs 0.0%(0/5) Tinnitus: 10.0%(1/10) vs 0.0%(0/5)</p>
<p>Merideth et al. 2008⁸⁷</p> <p>Anxiety</p>	<p>Inclusion criteria: DSM-IV diagnosis of GAD, HAM-A total score \geq20 with item 1 and item 2 scores \geq2, CGI-</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 1.46 (1.21 , 1.76)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Quetiapine</p> <p>Location: Not reported</p> <p>Trial: D1448C00010</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 854</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>S \geq4, MADRS \leq16</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 8 weeks vs Escitalopram 10 mg/days frequency not reported for 8 weeks vs Quetiapine 150 mg/days frequency not reported for 8 weeks vs Quetiapine 300 mg/days frequency not reported for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 4, 56 days</p>	
<p>Joyce et al. 2008⁹⁴</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: D1448C00009</p>	<p>Inclusion criteria: Not reported</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 50 mg/days frequency not</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 1.02 (0.85 , 1.21)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 710</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>reported for 8 weeks vs Quetiapine 150 mg/days frequency not reported for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 56 days</p>	
<p>Lohoff et al. 2010¹⁰⁰</p> <p>Anxiety</p> <p>Ziprasidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p>	<p>Inclusion criteria: >18 years old, meet DSM-IV criteria for GAD, have treatment failure of >= 1 adequate trial of an SSRI, SNRI, BZ, or combination HAM-A total score >= 16, CGI-S score >=4</p> <p>Exclusion criteria: Had a history of mania, bipolar disorder, schizophrenia, other psychotic disorders, had a history within 6 months of panic disorder, PTSD, major depression, OCD, social phobia, acute stress disorder, substance abuse, or other psychiatric diagnoses that may interfere with assessment, had clinical significant abnormalities, pregnant</p> <p>Interventions:</p>	<p>Results: Anxiety: Change in HAM-A (Total Score) at 8 weeks: Ziprasidone vs Placebo - WMD = -2.80 (-10.71 , 5.11)</p> <p>Anxiety: Change in HAM-A (Total Score) at 8 weeks: Ziprasidone vs Placebo - WMD = 2.83 (-2.26 , 7.92)</p> <p>Adverse Events: Placebo vs Ziprasidone Any Adverse Event: 85.7%(18/21) vs 87.8%(36/41) Blurred Vision: 0.0%(0/21) vs 4.9%(2/41) Constipation: 14.3%(3/21) vs 9.8%(4/41) Depression: 0.0%(0/21) vs 9.8%(4/41) Dermatitis: 9.5%(2/21) vs 0.0%(0/41) Diarrhea: 14.3%(3/21) vs 7.3%(3/41) Dizziness: 4.8%(1/21) vs 17.1%(7/41) Drowsiness: 28.6%(6/21) vs 51.2%(21/41)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: 73 Eligible: NR Entering: 62 Withdrawn: 12 Lost to follow-up: 3 Analyzed: 47</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Placebo 20-80 mg/days flexible dose for 8 weeks vs Ziprasidone 20-80 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Dry Mouth: 9.5%(2/21) vs 31.7%(13/41) Excitement: 4.8%(1/21) vs 14.6%(6/41) Headaches: 28.6%(6/21) vs 19.5%(8/41) Insomnia: 9.5%(2/21) vs 29.3%(12/41) Nausea: 9.5%(2/21) vs 14.6%(6/41) Stimulation: 19.0%(4/21) vs 43.9%(18/41) Tachycardia: 0.0%(0/21) vs 2.4%(1/41) Vivid Dreams: 0.0%(0/21) vs 4.9%(2/41) Weight Gain: 9.5%(2/21) vs 7.3%(3/41) Weight Loss: 4.8%(1/21) vs 2.4%(1/41)</p> <p>Withdrawals: Placebo vs Ziprasidone Withdrawals:9.5%(2/21) vs 31.7%(13/41) Withdrawals Due To Adverse Events:0.0%(0/21) vs 12.2%(5/41)</p>
<p>Katzman et al. 2011⁹³</p> <p>Anxiety</p> <p>Quetiapine</p> <p>Location: US, Canada, Western Europe, Eastern Europe, Australia/New Zealand, Asia</p> <p>Trial: platinum (D1448C00012)</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p>	<p>Inclusion criteria: 18-65 years old, DSM-IV-TR diagnosis of GAD, HAM-A total \geq 20, HAM-A item 1 and 2 \geq 2, CGI-S \geq 4</p> <p>Exclusion criteria: MADRS total \geq 17, DSM-IV Axis 1 disorder other than GAD within 6 months, schizophrenia and other psychotic disorders, substance abuse</p> <p>Interventions: Placebo 165.1 mg/days flexible dose for 69 days vs Quetiapine 162.8 (50-300) mg/days flexible dose for 107 days</p> <p>Run-in/wash-out period: Run-in: Quetiapine XR for 4-8 week(s). Patients who met the study criteria were randomized.</p>	<p>Results: Anxiety: Change in HAM-A (Mean Change) at 12 weeks: Quetiapine (varied) vs Placebo - WMD = -2.04 (-2.09 , -1.99)</p> <p>Adverse Events: Placebo Syncope: 0.5%(1/216) Placebo vs Quetiapine XR "treatment-Related Aes": 22.2%(48/216) vs 24.1%(52/216) Aes "potentially Related To Qt Prolongation Or Agranulocytosis": 0.0%(0/216) vs 0.0%(0/216) Fatal Saes: 0.0%(0/216) vs 0.0%(0/216) Insomnia: 13.9%(30/216) vs 3.2%(7/216) Neutropenia "possibly Tx Related": 0.0%(0/216) vs 0.5%(1/216) Non-Fatal Saes: 1.4%(3/216) vs 1.4%(3/216) Saes Reported By $>$1 Pt: 0.0%(0/216) vs 0.0%(0/216) Sedation, Mild To Moderate In Intensity: 0.0%(0/216) vs 2.3%(5/216) Somnolence, Mild To Moderate In Intensity: 0.0%(0/216) vs 0.9%(2/216) Worsening In Aims Total Score (Items 1-7): 5.1%(11/216) vs 2.3%(5/216) Worsening In Bars Global Assessment Score During Randomized Period: 4.6%(10/216) vs 2.8%(6/216) Worsening In Sas Total Score During Randomized Period: 7.9%(17/216) vs</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 432 Withdrawn: 53 Lost to follow-up: 14 Analyzed: 365</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>In Wash-out: Psychotropics for 28 day(s) were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 56, 364 days</p>	<p>5.6%(12/216) Quetiapine XR Syncope During The Randomized Period: 0.0%(0/216)</p> <p>Withdrawals: Placebo vs Placebo vs Quetiapine XR vs Quetiapine XR Headache Leading To Withdrawal:12.5%(27/216) vs 0.5%(1/216) vs 8.8%(19/216) vs 0.0%(0/216) Placebo vs Quetiapine XR Akathisia, Not Serious, Did Not Lead To Withdrawal During Randomized Period:0.9%(2/216) vs 0.5%(1/216) Alanine Aminotransferase Increased Leading To Withdrawal:0.5%(1/216) vs 0.0%(0/216) Any Ae Leading To Withdrawal:51.4%(111/216) vs 51.9%(112/216) Aspartate Aminotransferase Increased Leading To Withdrawal:0.5%(1/216) vs 0.0%(0/216) Bladder Cancer Leading To Withdrawal:0.0%(0/216) vs 0.5%(1/216) Epilepsy Leading To Withdrawal:0.0%(0/216) vs 0.5%(1/216) Fatigue Leading To Withdrawal:0.5%(1/216) vs 0.0%(0/216) Glycosylated Hemoglobin Increased Leading To Withdrawal:0.0%(0/216) vs 0.5%(1/216) Insomnia Leading To Withdrawal:1.9%(4/216) vs 0.0%(0/216) Nasopharyngitis Leading To Withdrawal:3.2%(7/216) vs 5.1%(11/216) Nausea Leading To Withdrawal:14.8%(32/216) vs 3.7%(8/216) Non-Fatal Saes Leading To Withdrawal:0.5%(1/216) vs 0.9%(2/216) Pancreatitis Leading To Withdrawal:0.5%(1/216) vs 0.0%(0/216) Pruritus Generalized Leading To Withdrawal:0.5%(1/216) vs 0.0%(0/216) Restlessness, Not Serious, Did Not Lead To Withdrawal During Randomized Period:0.0%(0/216) vs 1.9%(4/216) Somnolence Leading To Withdrawal:0.0%(0/216) vs 0.5%(1/216) Suicidal Behavior Leading To Withdrawal:0.0%(0/216) vs 0.5%(1/216) Tremor, Not Serious, Did Not Lead To Withdrawal During Randomized Period:0.5%(1/216) vs 0.9%(2/216) Withdrawals:55.1%(119/216) vs 25.0%(54/216) Withdrawals Due To Adverse Events:2.8%(6/216) vs 2.3%(5/216)</p>
<p>Altamura et al. 2011⁹⁰</p> <p>Anxiety</p> <p>Quetiapine</p>	<p>Inclusion criteria: GAD per DSM-IV and SCID</p> <p>Exclusion criteria: Concomitant treatment with benzodiazepines, severe medical disease, pregnancy, breast</p>	<p>Results: Anxiety: Change in HAM-A (% Responder) at 8 weeks: Quetiapine Augmentation vs Placebo - RR = 1.13 (0.88 , 1.45)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 20 Withdrawn: 0 Lost to follow-up: 0 Analyzed: 20</p> <p>Method of AE assessment: Not reported</p>	<p>feeding</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 50 (25-150) mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Depression, OCD, Personality Disorder</p> <p>Timing of outcome assessment: 56 days</p>	
<p>Mintzer et al. 2007¹⁰⁷</p> <p>Dementia/Agitation</p> <p>Aripiprazole</p> <p>Location: US, Canada, Australia/New Zealand, Latin America, South Africa</p>	<p>Inclusion criteria: Diagnosed with AD and delusions / hallucinations. Institutionalized, capable of self-locomotion, MMSE 6-22. NPI-NH score >=6</p> <p>Exclusion criteria: Delirium, amnesic disorder, bipolar disorder, schizophrenia, mood disorder, non-AD, depression with hallucinations / delusions, history of refractoriness to antipsychotics,</p>	<p>Results:</p> <p>Dementia: Change in CMAI (Agitation) at 10 weeks: Placebo vs Aripiprazole (all doses combined) - SMD = 0.31 (0.10 , 0.52)</p> <p>Dementia: Change in NPI psy (Psychosis) at 10 weeks: Placebo vs Aripiprazole (all doses combined) - SMD = 0.24 (0.03 , 0.45)</p> <p>Dementia: Change in NPI total (Total) at 10 weeks: Placebo vs Aripiprazole (all doses combined) - SMD = 0.16 (-0.05 , 0.37)</p> <p>Adverse Events:</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center, Long-term care facilities</p> <p>Jadad: 3</p> <p>Age: Mean: 56</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 654 Eligible: 487 Entering: 487 Withdrawn: 203 Lost to follow-up: 0 Analyzed: 284</p> <p>Method of AE assessment: Monitored, other</p>	<p>suicidal ideation, previous participation in aripiprazole trials, pregnancy.</p> <p>Interventions: Placebo for 10 weeks vs Aripiprazole 2 mg/days fixed single dose for 10 weeks vs Aripiprazole 5 mg/days fixed single dose for 10 weeks vs Aripiprazole 5-10 mg/days fixed single dose for 10 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56, 70 days</p>	<p>Aripiprazole 10 mg vs Aripiprazole 10 mg vs Aripiprazole 2 mg vs Aripiprazole 2 mg vs Aripiprazole 5 mg vs Aripiprazole 5 mg vs Placebo vs Placebo Infection: 5.6%(7/126) vs 5.6%(7/126) vs 7.6%(9/118) vs 7.6%(9/118) vs 4.9%(6/122) vs 4.9%(6/122) vs 4.1%(5/121) vs 4.1%(5/121) Aripiprazole 10 mg vs Aripiprazole 2 mg vs Aripiprazole 5 mg vs Placebo Abdominal Pain: 4.0%(5/126) vs 2.5%(3/118) vs 6.6%(8/122) vs 3.3%(4/121) Abnormal Gait: 4.0%(5/126) vs 1.7%(2/118) vs 7.4%(9/122) vs 0.8%(1/121) Accidental Injury: 19.8%(25/126) vs 29.7%(35/118) vs 23.8%(29/122) vs 19.0%(23/121) Agitation: 10.3%(13/126) vs 11.0%(13/118) vs 7.4%(9/122) vs 16.5%(20/121) Anorexia: 5.6%(7/126) vs 8.5%(10/118) vs 4.9%(6/122) vs 10.7%(13/121) Asthenia: 9.5%(12/126) vs 5.9%(7/118) vs 9.0%(11/122) vs 2.5%(3/121) Back Pain: 6.3%(8/126) vs 5.1%(6/118) vs 3.3%(4/122) vs 3.3%(4/121) Confusion: 4.8%(6/126) vs 2.5%(3/118) vs 7.4%(9/122) vs 4.1%(5/121) Conjunctivitis: 2.4%(3/126) vs 5.9%(7/118) vs 2.5%(3/122) vs 2.5%(3/121) Constipation: 3.2%(4/126) vs 5.1%(6/118) vs 4.9%(6/122) vs 5.0%(6/121) Coughing: 5.6%(7/126) vs 5.1%(6/118) vs 3.3%(4/122) vs 5.0%(6/121) Diarrhea: 8.7%(11/126) vs 5.9%(7/118) vs 6.6%(8/122) vs 5.8%(7/121) EPS: 7.1%(9/126) vs 7.6%(9/118) vs 7.4%(9/122) vs 5.8%(7/121) Ecchymosis: 8.7%(11/126) vs 8.5%(10/118) vs 4.9%(6/122) vs 9.9%(12/121) Edema: 1.6%(2/126) vs 5.1%(6/118) vs 3.3%(4/122) vs 1.7%(2/121) Edema, Peripheral: 8.7%(11/126) vs 10.2%(12/118) vs 5.7%(7/122) vs 8.3%(10/121) Extremity Pain: 9.5%(12/126) vs 6.8%(8/118) vs 9.0%(11/122) vs 5.8%(7/121) Headache: 7.1%(9/126) vs 4.2%(5/118) vs 4.1%(5/122) vs 3.3%(4/121) Incidence Of Clinically Significant Weight Gain: 4.0%(5/126) vs 6.8%(8/118) vs 4.1%(5/122) vs 5.8%(7/121) Incidence Of Clinically Significant Weight Loss: 11.1%(14/126) vs 10.2%(12/118) vs 13.1%(16/122) vs 14.9%(18/121) Increased Salivation: 1.6%(2/126) vs 1.7%(2/118) vs 7.4%(9/122) vs 0.8%(1/121) Insomnia: 4.8%(6/126) vs 9.3%(11/118) vs 5.7%(7/122) vs 8.3%(10/121) Lightheadedness: 3.2%(4/126) vs 5.1%(6/118) vs 4.1%(5/122) vs 0.0%(0/121) Rash: 7.9%(10/126) vs 9.3%(11/118) vs 9.0%(11/122) vs 8.3%(10/121) Skin Ulcer: 8.7%(11/126) vs 10.2%(12/118) vs 11.5%(14/122) vs 7.4%(9/121)</p>
<p>Mintzer et al. 2007¹⁰⁷</p> <p>Continued</p>		<p>Somnolence: 7.1%(9/126) vs 3.4%(4/118) vs 9.8%(12/122) vs 3.3%(4/121) Upper Respiratory Infection: 4.8%(6/126) vs 8.5%(10/118) vs 4.9%(6/122) vs 5.0%(6/121) Urinary Incontinence: 5.6%(7/126) vs 1.7%(2/118) vs 9.8%(12/122) vs 1.7%(2/121) Urinary-Tract Infection: 19.8%(25/126) vs 16.1%(19/118) vs 18.9%(23/122) vs 13.2%(16/121) Vomiting: 6.3%(8/126) vs 11.0%(13/118) vs 9.0%(11/122) vs 6.6%(8/121) Weight Loss: 4.0%(5/126) vs 5.1%(6/118) vs 4.9%(6/122) vs 3.3%(4/121)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
		<p>Withdrawals: Aripiprazole 10 mg vs Aripiprazole 2 mg vs Aripiprazole 5 mg vs Placebo Withdrawals:45.2%(57/126) vs 34.7%(41/118) vs 40.2%(49/122) vs 46.3%(56/121) Withdrawals Due To Adverse Events:24.6%(31/126) vs 7.6%(9/118) vs 18.0%(22/122) vs 13.2%(16/121)</p>
<p>Naber et al. 2007¹²⁸ Dementia/Agitation Risperidone Location: Not reported Trial: Not reported Funding source: Industry Design: RCT only Setting: Community practice Jadad: 3 Age: Mean: 49 Sex: Mixed Race: Not reported Screened: NR Eligible: NR Entering: 815 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p>	<p>Inclusion criteria: >=55, ICD-10 diagnosis of unspecified organic personality and behavioral disorder due to brain disease, damage and dysfunction, specific symptoms on PANSS</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 12 weeks vs Risperidone 0.5-4 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 84 days</p>	<p>Results: Dementia: No data</p> <p>Adverse Events: Placebo vs Risperidone Aes "related To Study Medication": 23.6%(48/203) vs 24.8%(152/612) Aes That Occurred In >5% Of Each Group: 0.0%(0/203) vs 0.0%(0/612) All Cardiovascular Adverse Events (Cae): 1.0%(2/203) vs 0.7%(4/612) Cardiovascular Adverse Event: Hospitalized After 74 D Treatment Due To Transient Speech Disorder And Disorientation; Diagnosed With Transient Ischemic Attack (Article Says "doubtful" It Was Related To Tx): 0.5%(1/203) vs 0.0%(0/612) Cardiovascular Adverse Event: Left Ventricular Failure And Acute Dextrocerebral Insult After 33 D Treatment; Died 2 D Later (Article Says Unrelated To Tx): 0.5%(1/203) vs 0.0%(0/612) Cardiovascular Adverse Event: Mild Unrest, Anxiety, Fear Of Drugs At End Of Week 3 Of Treatment; Could Not Speak For 1 D After 43 D Of Treatment; Suspected Transient Ischemic Attack; Medication Continued And Patient Completed Study (Article Says Unrelated To Tx): 0.0%(0/203) vs 0.2%(1/612) Cardiovascular Adverse Event: Mild Vertigo After 27 D Treatment, Diagnosed As Cerebral Circulatory Disorder With Suspicion Of Prolonged Reversible Ischemic Neurologic Deficit; Event Resolved After 6 D And Patient Continued Study (Article Says "possibly" Related To Tx): 0.0%(0/203) vs 0.2%(1/612) Cardiovascular Adverse Event: Paraesthesia In Extremities After 13 D Treatment, Transient Ischemic Attack Suspected And Patient, Hospitalized; Event Resolved After 36 D (Articles Says Unrelated To Tx): 0.0%(0/203) vs 0.2%(1/612) Cardiovascular Adverse Event: Transient Ischemic Attack After 89 D Treatment; Hospitalized For 6 D (Article Says Unrelated To Tx): 0.0%(0/203) vs 0.2%(1/612) Death During The Study Or Within 32 Days Of Study End (Article Says Unrelated To Study Medication): 2.5%(5/203) vs 0.8%(5/612) Eps Occurrence: 0.5%(1/203) vs 2.0%(12/612) Frequency Of Adverse Events: 31.5%(64/203) vs 35.0%(214/612)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Not reported		Withdrawals: Placebo vs Risperidone Withdrawals:10.3%(21/203) vs 9.8%(60/612) Withdrawals Due To Adverse Events:6.4%(13/203) vs 6.5%(40/612)
Zhong et al. 2007 ¹²² Dementia/Agitation Quetiapine Location: US Trial: Not reported Funding source: Industry Design: RCT only Setting: Multi-center, Long-term care facilities Jadad: 5 Age: Mean: 56 Sex: Mixed Race: Caucasian, African Ancestry, Hispanic, Asian/Pacific Islander, Other-NOS Screened: 435 Eligible: NR Entering: 333 Withdrawn: 118 Lost to follow-up: NR Analyzed: 215	Inclusion criteria: Institutionalized, diagnosed possible AD or vascular dementia, age >= 55, ambulatory, agitation that didn't result directly from participants medical condition, PANSS-EC total >= 14, one of the 5 PANSS-EC items >= 4. Exclusion criteria: History of schizophrenia, schizoaffective or bipolar disorder, agitation not related to dementia, failure to respond to a prior adequate AAP trial for agitation, unstable medical illness, abnormal ECG results. Interventions: Placebo for 10 weeks vs Quetiapine 25-100 mg/days fixed titration schedule for 10 weeks vs Quetiapine 25-200 mg/days fixed titration schedule for 10 weeks Run-in/wash-out period: Not reported Comorbidities: None Timing of outcome assessment: 7, 14, 28, 42, 56, 70 days	Results: Dementia: Change in NPI agitation (Agitation) at 10 weeks: Placebo vs Quetiapine (all doses combined) - SMD = -0.03 (-0.27 , 0.21) Dementia: Change in NPI psy (Psychosis) at 10 weeks: Placebo vs Quetiapine (all doses combined) - SMD = -0.03 (-0.27 , 0.21) Dementia: Change in NPI total (Total) at 10 weeks: Placebo vs Quetiapine (all doses combined) - SMD = 0.04 (-0.21 , 0.28) Adverse Events: Placebo vs Quetiapine 100 mg vs Quetiapine 200 mg Any Adverse Events: 80.4%(74/92) vs 80.6%(100/124) vs 84.6%(99/117) Cardiovascular: 4.3%(4/92) vs 1.6%(2/124) vs 5.1%(6/117) Constipation: 1.1%(1/92) vs 5.6%(7/124) vs 6.0%(7/117) Decreased Appetite: 3.3%(3/92) vs 1.6%(2/124) vs 6.0%(7/117) EPS: 5.4%(5/92) vs 4.8%(6/124) vs 6.8%(8/117) Fall: 26.1%(24/92) vs 25.8%(32/124) vs 26.5%(31/117) Gait Abnormalities: 0.0%(0/92) vs 4.8%(6/124) vs 5.1%(6/117) Headache: 3.3%(3/92) vs 5.6%(7/124) vs 3.4%(4/117) Lethargy: 3.3%(3/92) vs 6.5%(8/124) vs 11.1%(13/117) Nausea: 2.2%(2/92) vs 5.6%(7/124) vs 4.3%(5/117) Peripheral Edema: 6.5%(6/92) vs 7.3%(9/124) vs 5.1%(6/117) Sedation: 3.3%(3/92) vs 3.2%(4/124) vs 7.7%(9/117) Serious Adverse Events: 9.8%(9/92) vs 11.3%(14/124) vs 6.8%(8/117) Skin Laceration: 14.1%(13/92) vs 15.3%(19/124) vs 11.1%(13/117) Somnolence: 2.2%(2/92) vs 8.1%(10/124) vs 9.4%(11/117) Upper Respiratory Tract Infection: 4.3%(4/92) vs 4.8%(6/124) vs 5.1%(6/117) Urinary Tract Infection: 7.6%(7/92) vs 16.1%(20/124) vs 7.7%(9/117) Vomiting: 3.3%(3/92) vs 5.6%(7/124) vs 9.4%(11/117) Weight Decreased: 5.4%(5/92) vs 4.0%(5/124) vs 3.4%(4/117) Withdrawals: Placebo vs Quetiapine 100 mg vs Quetiapine 200 mg Withdrawals:34.8%(32/92) vs 34.7%(43/124) vs 36.8%(43/117) Withdrawals Due To Adverse Events:9.8%(9/92) vs 8.1%(10/124) vs 14.5%(17/117)

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Method of AE assessment: Monitored</p> <p>Streim et al. 2008¹⁰⁸</p> <p>Dementia/Agitation</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center, Long-term care facilities</p> <p>Jadad: 3</p> <p>Age: Mean: 59</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Asian/Pacific Islander</p> <p>Screened: 330 Eligible: 256 Entering: 256 Withdrawn: 105 Lost to follow-up: 0 Analyzed: 151</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Age 55-95 with AD, had psychotic symptoms for greater than/equal to 1month, institutionalized for more than 4 weeks, have a MMSE score 6-22 and NPI-NH>=6</p> <p>Exclusion criteria: Delirium or schizophrenia, mood disorder, continuous symptoms of psychosis before dementia, psychotic symptoms better accounted for any drug, depression with symptoms of psychosis, non-AD-type dementia, seizure, unstable thyroid pathology, suicide intention, potential to subject to AE, had participated in clinical study</p> <p>Interventions: Placebo for 10 weeks vs Aripiprazole 0.7-15 mg/days flexible dose for 10 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 7 day(s).</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56, 70 days</p>	<p>Results: Dementia: Change in CMAI (Agitation) at 10 weeks: Placebo vs Aripiprazole flexible dose - SMD = 0.30 (0.05 , 0.55)</p> <p>Dementia: Change in NPI psy (Psychosis) at 10 weeks: Placebo vs Aripiprazole flexible dose - SMD = -0.02 (-0.27 , 0.23)</p> <p>Dementia: Change in NPI total (Total) at 10 weeks: Placebo vs Aripiprazole flexible dose - SMD = 0.36 (0.11 , 0.61)</p> <p>Adverse Events: Aripiprazole vs Placebo Accidental Injury: 20.6%(27/131) vs 28.8%(36/125) Agitation: 7.6%(10/131) vs 12.0%(15/125) Asthenia: 12.2%(16/131) vs 6.4%(8/125) Cerebrovascular Accident: 0.0%(0/131) vs 0.8%(1/125) EPS-Related Adverse Events: 5.3%(7/131) vs 4.0%(5/125) Ecchymosis: 12.2%(16/131) vs 12.8%(16/125) Orthostatic Events (Hypotension Or Syncope): 3.1%(4/131) vs 4.8%(6/125) Potentially Clinically Significant Increases In QTc Interval: 1.5%(2/131) vs 0.8%(1/125) Potentially Significant Low Hemoglobin Levels: 10.7%(14/131) vs 6.4%(8/125) Rash: 9.9%(13/131) vs 12.0%(15/125) Serious Adverse Events Of Accidental Injury: 1.5%(2/131) vs 4.8%(6/125) Somnolence: 13.7%(18/131) vs 4.0%(5/125) Total Serious Adverse Events: 12.2%(16/131) vs 13.6%(17/125) Ulcer Skin: 9.2%(12/131) vs 12.0%(15/125) Urinary Tract Infection: 13.7%(18/131) vs 10.4%(13/125) Vomiting: 9.9%(13/131) vs 8.0%(10/125)</p> <p>Withdrawals: Aripiprazole vs Placebo Death During The Study Or Within 30 Days Of Withdrawal:2.3%(3/131) vs 2.4%(3/125) Withdrawals:33.6%(44/131) vs 48.8%(61/125) Withdrawals Due To Abnormal Lab Test Results:0.0%(0/131) vs 0.0%(0/125) Withdrawals Due To Adverse Events:13.0%(17/131) vs 8.0%(10/125) Withdrawals Due To ECG Abnormality Including Prolongation Of The QTc Interval:0.0%(0/131) vs 0.0%(0/125) Withdrawals Due To Weight Loss:0.0%(0/131) vs 0.0%(0/125)</p>

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<p>Rappaport et al. 2009¹⁰⁹</p> <p>Dementia/Agitation</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 80</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Other-NOS</p> <p>Screened: 150 Eligible: 129 Entering: 116 Withdrawn: 2 Lost to follow-up: 0 Analyzed: 115</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Diagnosed with AD, vascular, or mixed dementia, in healthcare facilities, moderate to severe acute exacerbation of agitated behaviors, able to comply with protocol</p> <p>Exclusion criteria: Other major psychiatric disorders, history of neuroleptic malignant syndrome, seizure, stroke, severe head trauma</p> <p>Interventions: Placebo for 24 hours vs Aripiprazole 5 mg/Not reported average final dose for 24 hours vs Aripiprazole 10 mg/Not reported average final dose for 24 hours</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 2, 4, 6, 12, 24 hours</p>	<p>Results: Dementia: Change in ACES (Agitation) at 0.14 weeks: Placebo vs Aripiprazole (all doses combined) - SMD = 5.00 (4.24 , 5.76)</p> <p>Adverse Events: Aripiprazole 10 mg vs Aripiprazole 15 mg vs Aripiprazole 5 mg vs Placebo Agitation: 1.3%(1/78) vs 0.0%(0/13) vs 0.0%(0/12) vs 7.7%(2/26) Any Adverse Event: 52.6%(41/78) vs 69.2%(9/13) vs 50.0%(6/12) vs 30.8%(8/26) Cerebrovascular AE (Acute Stroke) 16 Days After Treatment (Judged Unlikely To Be Treatment-Related): 1.3%(1/78) vs 0.0%(0/13) vs 0.0%(0/12) vs 0.0%(0/26) Clinically Significant Vital Signs Or Electrocardiograms: 0.0%(0/78) vs 0.0%(0/13) vs 0.0%(0/12) vs 0.0%(0/26) Death 24 Days After Treatment (Not Reasonably Linked To Study Medication): 1.3%(1/78) vs 0.0%(0/13) vs 0.0%(0/12) vs 0.0%(0/26) Dementia: 0.0%(0/78) vs 0.0%(0/13) vs 25.0%(3/12) vs 0.0%(0/26) EPS: 0.0%(0/78) vs 0.0%(0/13) vs 0.0%(0/12) vs 0.0%(0/26) Electrocardiogram Change: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Fall: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 3.8%(1/26) Femoral Neck Fracture: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Insomnia: 2.6%(2/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Irregular Heart Rate: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Lethargy: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Pyrexia: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Serious AE: 7.7%(6/78) vs 7.7%(1/13) vs 25.0%(3/12) vs 7.7%(2/26) Skin Laceration: 1.3%(1/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 7.7%(2/26) Somnolence: 38.5%(30/78) vs 38.5%(5/13) vs 16.7%(2/12) vs 7.7%(2/26) Vomiting: 3.8%(3/78) vs 0.0%(0/13) vs 8.3%(1/12) vs 0.0%(0/26)</p> <p>Withdrawals: Aripiprazole 10 mg vs Aripiprazole 15 mg vs Aripiprazole 5 mg vs Placebo Femoral Neck Fracture Resulting From A Fall On Wet Floor And Leading To Withdrawal: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26) Withdrawals: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 3.8%(1/26) Withdrawals Due To Adverse Events: 0.0%(0/78) vs 7.7%(1/13) vs 0.0%(0/12) vs 0.0%(0/26)</p>
<p>Paleacu et al. 2008¹²³</p> <p>Dementia/Agitation</p> <p>Quetiapine</p>	<p>Inclusion criteria: AD with BPSD, age > 50, MMSE < 24, NPI > 6 on any item</p> <p>Exclusion criteria:</p>	<p>Results: Dementia: Change in NPI agitation (Agitation) at 6 weeks: Placebo vs Quetiapine - SMD = -0.48 (-1.11 , 0.15)</p> <p>Adverse Events:</p>

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<p>Location: Israel</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 44 Eligible: 40 Entering: 40 Withdrawn: 12 Lost to follow-up: 1 Analyzed: 27</p> <p>Method of AE assessment: Monitored, reported spontaneously by patient</p>	<p>Other types of dementia, malignancy, heart disease, women of child-bearing potential, alcohol or drug abuse</p> <p>Interventions: Placebo for 6 weeks vs Quetiapine 50-300 mg/days flexible dose for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42 days</p>	<p>Quetiapine vs Placebo</p> <p>Akathisia: 0.0%(0/20) vs 5.0%(1/20)</p> <p>Confusion Urinary Tract Infection: 5.0%(1/20) vs 0.0%(0/20)</p> <p>Diarrhea: 0.0%(0/20) vs 5.0%(1/20)</p> <p>Dizziness: 0.0%(0/20) vs 5.0%(1/20)</p> <p>Dry Mouth: 5.0%(1/20) vs 0.0%(0/20)</p> <p>Edema: 0.0%(0/20) vs 5.0%(1/20)</p> <p>Elevated Systolic Bp (190/90): 5.0%(1/20) vs 0.0%(0/20)</p> <p>Falls: 0.0%(0/20) vs 10.0%(2/20)</p> <p>Headaches: 5.0%(1/20) vs 0.0%(0/20)</p> <p>Parkinsonism: 5.0%(1/20) vs 5.0%(1/20)</p> <p>Sedation: 5.0%(1/20) vs 0.0%(0/20)</p> <p>Tremor: 0.0%(0/20) vs 5.0%(1/20)</p> <p>Withdrawals: Quetiapine vs Placebo Withdrawals:40.0%(8/20) vs 25.0%(5/20) Withdrawals Due To Adverse Events:5.0%(1/20) vs 5.0%(1/20)</p>
<p>Mintzer et al. 2006¹²⁹</p> <p>Dementia/Agitation</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: >= 55 years old, residents of nursing homes or long-term care facilities, mobile, met the criteria for psychosis of AD, in need of treatment with an atypical antipsychotic, scored >=2 on any item of the BEHAVE-AD psychosis subscale, MMSE 5-23</p> <p>Exclusion criteria:</p>	<p>Results:</p> <p>Dementia: Change in BEHAVE-AD agg (Agitation) at 8 weeks: Placebo vs Risperidone - SMD = 0.04 (-0.16 , 0.23)</p> <p>Dementia: Change in BEHAVE-AD psy (Psychosis) at 8 weeks: Placebo vs Risperidone - SMD = 0.17 (-0.02 , 0.36)</p> <p>Dementia: Change in BEHAVE-AD total (Total) at 8 weeks: Placebo vs Risperidone - SMD = -0.01 (-0.21 , 0.18)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center, Long-term care facilities</p> <p>Jadad: 3</p> <p>Age: Mean: 83</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 560 Eligible: 473 Entering: 473 Withdrawn: 117 Lost to follow-up: 1 Analyzed: 354</p> <p>Method of AE assessment: Monitored</p>	<p>Recently treated with neuroleptic injections, had other medical conditions that diminish cognition, had other psychiatric disorders that produce psychotic symptoms, patients with epilepsy, cancer, unstable medical conditions</p> <p>Interventions: Placebo for 8 weeks vs Risperidone 0.5-2.5 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: Placebo for 1-16 day(s). Patients still eligible after washout were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56 days</p>	<p>Adverse Events: Placebo vs Risperidone Agitation: 6.7%(16/238) vs 8.1%(19/235) Any Adverse Event: 63.9%(152/238) vs 74.5%(175/235) Death: 0.0%(0/238) vs 0.9%(2/235) Edema-Related: 4.6%(11/238) vs 5.1%(12/235) Extrapyramidal Symptoms-Related: 3.4%(8/238) vs 8.5%(20/235) Fall: 12.6%(30/238) vs 11.1%(26/235) Glucose-Related: 2.1%(5/238) vs 1.7%(4/235) Hematoma: 5.0%(12/238) vs 3.4%(8/235) Injury: 10.5%(25/238) vs 9.4%(22/235) Insomnia: 5.9%(14/238) vs 5.5%(13/235) Potentially Prolactin-Related: 0.0%(0/238) vs 0.0%(0/235) Serious Adverse Event: 13.0%(31/238) vs 14.0%(33/235) Somnolence: 4.6%(11/238) vs 16.2%(38/235) Stroke: 0.4%(1/238) vs 0.4%(1/235) Tardive Dyskinesia: 0.0%(0/238) vs 0.0%(0/235) Transient Ischemic Attack: 0.0%(0/238) vs 1.3%(3/235) Urinary Tract Infection: 10.1%(24/238) vs 9.4%(22/235)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:24.8%(59/238) vs 25.1%(59/235) Withdrawals Due To Adverse Events:10.1%(24/238) vs 10.6%(25/235)</p>
<p>Cutler et al. 2009¹⁷¹</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p>	<p>Inclusion criteria: 18-65 years old, diagnosed MDD, HAM-D total score >=22, HAM-D item 1 score >=>= at enrollment and randomization</p> <p>Exclusion criteria: DSM-IV AXIS I/II disorders duration of current MDD >= 12 months or <=4 weeks, inadequate response to at least 6 weeks of treatment with 2 or more classes of antidepressants during current episode, clinically significant medical illness, psychotic</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Quetiapine vs Placebo - RR = 1.43 (1.03 , 2.06)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Quetiapine vs Placebo - RR = 1.51 (1.20 , 1.91)</p> <p>Adverse Events: Duloxetine 60 mg/d vs Placebo vs Quetiapine 150 mg/d vs Quetiapine 300 mg/d >= 7% Increase In Body Weight: 0.7%(1/151) vs 0.0%(0/157) vs 2.0%(3/152) vs 3.3%(5/152) Abnormal Dreams: 2.6%(4/151) vs 0.6%(1/157) vs 6.6%(10/152) vs 2.0%(3/152)</p>

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<p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 912</p> <p>Eligible: NR</p> <p>Entering: 612</p> <p>Withdrawn: 138</p> <p>Lost to follow-up: 32</p> <p>Analyzed: 370</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>feature</p> <p>Interventions: Placebo for 6 weeks vs Quetiapine 50-150 mg/days fixed titration schedule for 6 weeks vs Quetiapine 50-300 mg/days fixed titration schedule for 6 weeks vs Haldol 60 mg/days fixed single dose for 6 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 7-28 day(s). Eligible patents were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56 days</p>	<p>Clinically Important Elevated Glucose (=126 mg/dL) at endpoint: 0.7%(1/151) vs 0.6%(1/157) vs 2.0%(3/152) vs 3.9%(6/152)</p> <p>Constipation: 11.3%(17/151) vs 6.4%(10/157) vs 5.9%(9/152) vs 8.6%(13/152)</p> <p>Decreased Appetite: 5.3%(8/151) vs 0.6%(1/157) vs 3.3%(5/152) vs 0.0%(0/152)</p> <p>Diarrhea: 10.6%(16/151) vs 6.4%(10/157) vs 4.6%(7/152) vs 2.6%(4/152)</p> <p>Dizziness: 16.6%(25/151) vs 10.8%(17/157) vs 14.5%(22/152) vs 19.1%(29/152)</p> <p>Dry Mouth: 18.5%(28/151) vs 8.9%(14/157) vs 33.6%(51/152) vs 38.2%(58/152)</p> <p>Dyspepsia: 5.3%(8/151) vs 3.2%(5/157) vs 3.9%(6/152) vs 5.3%(8/152)</p> <p>Fatigue: 6.6%(10/151) vs 0.0%(0/157) vs 2.6%(4/152) vs 5.3%(8/152)</p> <p>Headache: 17.9%(27/151) vs 10.2%(16/157) vs 10.5%(16/152) vs 9.2%(14/152)</p> <p>Hyperhidrosis: 7.3%(11/151) vs 0.6%(1/157) vs 0.0%(0/152) vs 0.0%(0/152)</p> <p>Increased Appetite: 2.0%(3/151) vs 1.9%(3/157) vs 5.9%(9/152) vs 3.9%(6/152)</p> <p>Insomnia: 14.6%(22/151) vs 7.0%(11/157) vs 1.3%(2/152) vs 1.3%(2/152)</p> <p>Irritability: 0.0%(0/151) vs 4.5%(7/157) vs 1.3%(2/152) vs 5.9%(9/152)</p> <p>Nausea: 35.8%(54/151) vs 9.6%(15/157) vs 10.5%(16/152) vs 5.3%(8/152)</p> <p>Pollakiuria: 5.3%(8/151) vs 1.3%(2/157) vs 3.3%(5/152) vs 2.0%(3/152)</p> <p>Sedation: 15.9%(24/151) vs 5.1%(8/157) vs 38.8%(59/152) vs 36.8%(56/152)</p> <p>Somnolence: 12.6%(19/151) vs 7.0%(11/157) vs 24.3%(37/152) vs 27.0%(41/152)</p> <p>Upper Respiratory Tract Infection: 4.0%(6/151) vs 7.0%(11/157) vs 2.0%(3/152) vs 2.6%(4/152)</p> <p>Vision Blurred: 2.6%(4/151) vs 1.9%(3/157) vs 5.3%(8/152) vs 5.3%(8/152)</p> <p>Withdrawals: Duloxetine 60 mg/d vs Placebo vs Quetiapine 150 mg/d vs Quetiapine 300 mg/d Withdrawals:30.5%(46/151) vs 21.0%(33/157) vs 34.2%(52/152) vs 25.7%(39/152) Withdrawals Due To Adverse Events:13.2%(20/151) vs 4.5%(7/157) vs 19.7%(30/152) vs 15.1%(23/152) Withdrawals Due To Of Death:0.0%(0/151) vs 0.0%(0/157) vs 0.7%(1/152) vs 0.0%(0/152)</p>
<p>Weisler et al. 2009¹⁷²</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p>	<p>Inclusion criteria: 18-65, output, MDD, HAM-D item 17>=22, HAM-D item 1>=2</p> <p>Exclusion criteria: Other axis I disorders during prior 6 month, Axis II impacting status, current MDD episode > 12 months or <4 weeks, inadequate response to adequate antidepressants treatment with >= 2 classes of antidepressants, medical illness, suicide or homicide risk</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 6 weeks: Quetiapine vs Placebo - RR = 1.27 (0.89 , 1.82)</p> <p>Depression: Change in MADRS (% Responder) at 6 weeks: Quetiapine vs Placebo - RR = 1.58 (1.24 , 2.02)</p> <p>Adverse Events: Placebo vs Quetiapine 150mg vs Quetiapine 300mg vs Quetiapine 50mg Any Adverse Event: 67.9%(125/184) vs 87.1%(155/178) vs 87.7%(157/179) vs 80.2%(146/182) Back Pain: 2.2%(4/184) vs 5.6%(10/178) vs 5.0%(9/179) vs 1.6%(3/182)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 5</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 1075 Eligible: 723 Entering: 723 Withdrawn: 127 Lost to follow-up: 85 Analyzed: 511</p> <p>Method of AE assessment: Monitored</p>	<p>Interventions: Placebo for 6 weeks vs Quetiapine 50 mg/days fixed titration schedule for 6 weeks vs Quetiapine 50-150 mg/days fixed titration schedule for 6 weeks vs Quetiapine 50-300 mg/days fixed titration schedule for 6 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 4, 7, 14, 28, 42 days</p>	<p>Constipation: 2.7%(5/184) vs 8.4%(15/178) vs 8.9%(16/179) vs 7.1%(13/182) Death: 0.0%(0/184) vs 0.0%(0/178) vs 0.0%(0/179) vs 0.0%(0/182) Diarrhea: 8.7%(16/184) vs 6.2%(11/178) vs 3.4%(6/179) vs 6.6%(12/182) Dizziness: 5.4%(10/184) vs 10.7%(19/178) vs 10.6%(19/179) vs 8.8%(16/182) Dry Mouth: 8.7%(16/184) vs 37.1%(66/178) vs 41.3%(74/179) vs 22.0%(40/182) Dyspepsia: 2.7%(5/184) vs 5.6%(10/178) vs 2.8%(5/179) vs 2.2%(4/182) Fatigue: 4.3%(8/184) vs 7.9%(14/178) vs 6.1%(11/179) vs 6.0%(11/182) Headache: 14.7%(27/184) vs 13.5%(24/178) vs 14.5%(26/179) vs 12.1%(22/182) Increased Appetite: 3.8%(7/184) vs 5.1%(9/178) vs 4.5%(8/179) vs 4.4%(8/182) Insomnia: 7.6%(14/184) vs 6.7%(12/178) vs 6.7%(12/179) vs 4.9%(9/182) Irritability: 3.8%(7/184) vs 5.6%(10/178) vs 3.4%(6/179) vs 6.0%(11/182) Myalgia: 1.6%(3/184) vs 7.3%(13/178) vs 2.2%(4/179) vs 4.4%(8/182) Nausea: 6.0%(11/184) vs 8.4%(15/178) vs 8.9%(16/179) vs 7.7%(14/182) Sedation: 6.0%(11/184) vs 35.4%(63/178) vs 30.7%(55/179) vs 26.9%(49/182) Somnolence: 10.9%(20/184) vs 19.7%(35/178) vs 29.1%(52/179) vs 18.1%(33/182) Vomiting: 2.2%(4/184) vs 2.2%(4/178) vs 6.7%(12/179) vs 1.6%(3/182)</p> <p>Withdrawals: Placebo vs Quetiapine 150mg vs Quetiapine 300mg vs Quetiapine 50mg Withdrawals:27.2%(50/184) vs 30.9%(55/178) vs 33.0%(59/179) vs 26.4%(48/182) Withdrawals Due To Adverse Events:6.0%(11/184) vs 14.0%(25/178) vs 19.0%(34/179) vs 8.2%(15/182)</p>
<p>Chaput et al. 2008¹⁵⁸</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p>	<p>Inclusion criteria: MD, HRSD >= 20, CGI-S >=4, 2 classes of antidepressants</p> <p>Exclusion criteria: Suicide risk, pregnant, breast feeding, not on birth control for 3 month prior, bipolar, schizophrenia, personality disorder, panic, anxiety, OCD, somatoformor organic mental disorder, anorexia, bulimia, substance abuse, other psychotropics, unstable medical illness</p> <p>Interventions: Placebo 12.5-200 mg/days flexible dose for 12 weeks vs</p>	<p>Results: Depression: Only data on placebo group reported</p> <p>Adverse Events: Quetiapine/CBT vs. Placebo/CBT Dry Mouth: 36.4%(4/11) vs 9.1%(1/11) Gastrointestinal Discomfort: 18.2%(2/11) vs 27.3%(3/11) Headache: 36.4%(4/11) vs 9.1%(1/11) Insomnia: 45.5%(5/11) vs 18.2%(2/11) Labile Hypertension: 9.1%(1/11) vs 9.1%(1/11) Mild Akathisia And Muscle Rigidity: 0.0%(0/11) vs 9.1%(1/11) Nausea: 18.2%(2/11) vs 18.2%(2/11) Somnolence: 63.6%(7/11) vs 9.1%(1/11)</p> <p>Withdrawals: Quetiapine/CBT vs Placebo/CBT</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 2</p> <p>Age: Mean: 23</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: 40 Eligible: 24 Entering: 22 Withdrawn: NR Lost to follow-up: NR Analyzed: 15</p> <p>Method of AE assessment: Monitored</p>	<p>Quetiapine 12.5-200 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Run-in: Lithium for 3 week(s). Non-responders were randomized. In Wash-out: No drug for 8 day(s). Patients still eligible after washout were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 21, 28, 42, 56, 70, 84, 98 days</p>	<p>Possible Anomaly Detected At The Week 10 Electrocardiogram That Was Ultimately Found To Be A False Positive Result Leading To Withdrawal:9.1%(1/11) vs 0.0%(0/11) Withdrawals:9.1%(1/11) vs 54.5%(6/11) Withdrawals Due To Adverse Events:0.0%(0/11) vs 0.0%(0/11)</p>
<p>AstraZeneca 2008¹⁷³</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US, Canada, Western Europe, South Africa</p> <p>Trial: AMETHYST</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 19</p>	<p>Inclusion criteria: Age 18-65, with DSM-IV diagnosis of MDD together with an acute depressed episode confirmed by MINI, have a current episode of depression ≥ 4 weeks and < 12 months in duration, HAM-D total score ≥ 20, HAM-D item 1 score ≥ 2, MADRS score ≤ 12, CGI-S score ≤ 3</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo 50-300 mg/days flexible dose for 52 weeks vs Quetiapine 50-300 mg/days flexible dose for 52 weeks</p> <p>Run-in/wash-out period: Run-in: Antipsychotics for 26 week(s). Patients who met the study criteria were randomized.</p>	<p>Results: Depression: Change in MADRS (Total) at 52 weeks: Quetiapine vs Placebo - WMD = -1.88 (-1.91 , -1.85)</p> <p>Adverse Events: Placebo Serious AE Leading To Death (Hypertension): 0.3%(1/385) Placebo vs Quetiapine "drug-Related Ae": 28.3%(109/385) vs 33.0%(129/391) ≥ 15 bpm Increases In Heart Rate: 6.5%(25/385) vs 10.2%(40/391) $\geq 7\%$ Increase In Weight: 2.9%(11/385) vs 5.4%(21/391) AE Potentially Related To Neutropenia Or Agranulocytosis: 0.0%(0/385) vs 0.0%(0/391) AE Potentially Related To Qt Prolongation: 0.0%(0/385) vs 0.0%(0/391) AEs Potentially Related To Nausea And Vomiting: 10.9%(42/385) vs 4.9%(19/391) Anxiety: 2.6%(10/385) vs 1.3%(5/391) Any AE: 60.5%(233/385) vs 62.9%(246/391) Arthralgia: 2.3%(9/385) vs 4.9%(19/391) Back Pain: 2.6%(10/385) vs 3.8%(15/391) Blood Pressure Increased: 0.5%(2/385) vs 2.3%(9/391) Constipation: 0.3%(1/385) vs 2.0%(8/391) Decreases ≥ 20 Millimeters Of Mercury In Orthostatic Systolic Blood Pressure: 6.2%(24/385) vs 11.5%(45/391)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 776 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 364 days</p>	<p>Diarrhea: 6.8%(26/385) vs 5.4%(21/391) Disturbance In Attention: 0.0%(0/385) vs 0.0%(0/391) Dizziness: 4.4%(17/385) vs 6.6%(26/391) Dry Mouth: 1.6%(6/385) vs 3.6%(14/391) Dyspepsia: 0.0%(0/385) vs 0.0%(0/391) Edema Peripheral: 0.0%(0/385) vs 0.0%(0/391) Fatigue: 2.6%(10/385) vs 4.3%(17/391) Headache: 11.4%(44/385) vs 6.9%(27/391) Incidence Of Syncope: 0.0%(0/385) vs 0.8%(3/391) Increased Appetite: 0.0%(0/385) vs 0.0%(0/391) Increases =15 Bpm In Supine Pulse: 19.2%(74/385) vs 28.1%(110/391) Insomnia: 14.8%(57/385) vs 5.6%(22/391) Irritability: 3.1%(12/385) vs 0.8%(3/391) Lethargy: 0.0%(0/385) vs 0.0%(0/391) Musculoskeletal Pain: 1.3%(5/385) vs 2.0%(8/391) Myalgia: 1.3%(5/385) vs 2.3%(9/391) Nasopharyngitis: 6.5%(25/385) vs 7.2%(28/391) Nausea: 9.9%(38/385) vs 3.6%(14/391) Pain In Extremity: 2.1%(8/385) vs 1.5%(6/391) QTcF Values >=450ms: 2.6%(10/385) vs 2.6%(10/391) Restlessness: 0.0%(0/385) vs 0.0%(0/391) Sedation: 0.3%(1/385) vs 2.6%(10/391) Serious Ae, All: 2.1%(8/385) vs 2.0%(8/391) Sinusitis: 2.3%(9/385) vs 3.1%(12/391) Somnolence: 0.0%(0/385) vs 3.8%(15/391) Tx Emergent Shift From <3 To =3 Metabolic Risk Factors: 12.7%(49/385) vs 17.6%(69/391) Upper Respiratory Tract Infection: 4.2%(16/385) vs 3.8%(15/391) Urinary Tract Infection: 1.0%(4/385) vs 2.3%(9/391) Vision Blurred: 0.0%(0/385) vs 0.0%(0/391) Vomiting: 2.3%(9/385) vs 2.0%(8/391) Weight Increased: 1.6%(6/385) vs 9.7%(38/391) Quetiapine Serious Ae Leading To Death: 0.0%(0/391)</p> <p>Withdrawals: Placebo vs Quetiapine Withdrawals Due To Adverse Events:5.2%(20/385) vs 6.4%(25/391)</p>
<p>AstraZeneca 2008¹⁶⁹</p> <p>Depression</p>	<p>Inclusion criteria: Age >=66, DSM-IV diagnosis of MDD confirmed by MINI. HAM-D total score >=22,</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 9 weeks: Quetiapine vs Placebo - RR = 2.48 (1.70 , 3.62)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Quetiapine</p> <p>Location: US, Eastern Europe, Latin America</p> <p>Trial: SAPPHERE</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 66</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Other-NOS</p> <p>Screened: NR Eligible: NR Entering: 338 Withdrawn: NR Lost to follow-up: NR Analyzed: 224</p> <p>Method of AE assessment: Monitored</p>	<p>HAM-D item 1 score ≥ 2 at both enrollment and randomization.</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo 50-300 mg/days flexible dose for 9 weeks vs Quetiapine 50-300 mg/days flexible dose for 9 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 28 day(s). Patients still eligible after washout were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 63 days</p>	<p>Depression: Change in MADRS (% Responder) at 9 weeks: Quetiapine vs Placebo - RR = 2.11 (1.63 , 2.71)</p> <p>Adverse Events: Placebo vs Quetiapine "drug-Related Ae": 39.5%(68/172) vs 62.7%(104/166) $\geq 7\%$ Weight Decrease: 1.2%(2/172) vs 0.0%(0/166) $\geq 7\%$ Weight Increase: 0.6%(1/172) vs 0.0%(0/166) AE Potentially Related To Diabetes (Blood Glucose Increased In Patient Who Was Being Treated For Type II Diabetes Prior To And During The Study): 0.0%(0/172) vs 0.6%(1/166) AE Potentially Related To Suicidality: 0.6%(1/172) vs 0.6%(1/166) AEs Potentially Related To Qt Prolongation, Neutropenia/Agranulocytosis, Syncope, Sexual Dysfunction, Or Cerebrovascular Accidents (Eva): 0.0%(0/172) vs 0.0%(0/166) Abdominal Pain Upper: 2.3%(4/172) vs 3.0%(5/166) Any AE: 61.0%(105/172) vs 80.7%(134/166) Asthenia: 0.6%(1/172) vs 3.6%(6/166) Back Pain: 1.2%(2/172) vs 2.4%(4/166) Clinically Important Shift To Low Neutrophil Count At End of Treatment: 0.0%(0/172) vs 1.2%(2/166) Constipation: 2.3%(4/172) vs 6.0%(10/166) Diarrhea: 7.0%(12/172) vs 5.4%(9/166) Dizziness: 15.1%(26/172) vs 19.3%(32/166) Dry Mouth: 10.5%(18/172) vs 20.5%(34/166) Dysgeusia: 0.6%(1/172) vs 2.4%(4/166) Edema Peripheral: 2.3%(4/172) vs 0.0%(0/166) Extrapyramidal Disorder: 0.6%(1/172) vs 3.6%(6/166) Extrapyramidal Symptoms (EPS) Through The End Of The Study: 2.3%(4/172) vs 9.0%(15/166) Fatigue: 4.1%(7/172) vs 7.8%(13/166) Headache: 16.3%(28/172) vs 21.1%(35/166) Hypertension: 2.3%(4/172) vs 1.2%(2/166) Hypotension: 0.0%(0/172) vs 2.4%(4/166) Hypothyroidism: 0.0%(0/172) vs 0.0%(0/166) Insomnia: 5.8%(10/172) vs 7.8%(13/166) Nasopharyngitis: 3.5%(6/172) vs 1.2%(2/166) Nausea: 4.7%(8/172) vs 5.4%(9/166) Pain In Extremity: 1.2%(2/172) vs 2.4%(4/166) Sedation: 1.2%(2/172) vs 4.8%(8/166) Serious AE Leading To Death: 0.0%(0/172) vs 0.0%(0/166) Serious Ae, All: 1.2%(2/172) vs 2.4%(4/166)</p>

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		<p>Somnolence: 8.1%(14/172) vs 33.1%(55/166) Tachycardia: 2.3%(4/172) vs 1.2%(2/166) Treatment-Emergent Clinically Important Triglyceride Values: 5.8%(10/172) vs 13.9%(23/166) Treatment-Emergent Hypothyroidism Based On Clinically Important High Thyroid-Stimulating Hormone (Tsh) Values In Combination With Clinically Important Low Thyroxine (T4) Values: 0.0%(0/172) vs 0.0%(0/166) Treatment-Emergent Shift From <3 To =3 Metabolic Risk Factors: 13.4%(23/172) vs 5.4%(9/166) Weight Increased: 4.1%(7/172) vs 5.4%(9/166) Worsening Of Aims Total Score: 4.7%(8/172) vs 9.0%(15/166) Worsening Of Bars Global Scores: 1.2%(2/172) vs 1.2%(2/166) Worsening Of Sas Total Score: 8.1%(14/172) vs 13.9%(23/166) Quetiapine Extrapyramidal Symptoms (EPS) Only During The Treatment Period: 7.2%(12/166)</p> <p>Withdrawals: Placebo vs Quetiapine Withdrawals:33.7%(58/172) vs 33.7%(56/166) Withdrawals Due To Adverse Events:4.1%(7/172) vs 9.6%(16/166)</p>
<p>AstraZeneca2007¹⁶⁸ Depression Quetiapine Location: Canada, Western Europe, Asia, Latin America, South Africa Trial: AMBER D1448C00004 Funding source: Industry Design: RCT only Setting: Multi-center</p>	<p>Inclusion criteria: 18-65 years old, DSM-IV diagnosis of MDD, HAM-D score >=22, HAM-D item 1 score >=2</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 9 weeks vs Quetiapine 50-300 mg/days flexible dose for 9 weeks vs Escitalopram 10-20 mg/days flexible dose for 9 weeks</p> <p>Run-in/wash-out period: Wash-out: No drug for 7-28 day(s). Patients still eligible after washout were randomized.</p> <p>Comorbidities:</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 8 weeks: Quetiapine vs Placebo - RR = 1.01 (0.75 , 1.37)</p> <p>Depression: Change in MADRS (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 1.18 (0.97 , 1.45)</p> <p>Adverse Events: Escitalopram vs Placebo vs Quetiapine "drug-Related Ae": 67.5%(106/157) vs 51.6%(81/157) vs 79.6%(125/157) Abdominal Distension: 3.2%(5/157) vs 2.5%(4/157) vs 2.5%(4/157) Abdominal Pain: 3.8%(6/157) vs 3.2%(5/157) vs 4.5%(7/157) Abdominal Pain Upper: 3.2%(5/157) vs 3.8%(6/157) vs 5.7%(9/157) Akathisia: 3.2%(5/157) vs 0.6%(1/157) vs 1.3%(2/157) Anxiety: 4.5%(7/157) vs 2.5%(4/157) vs 7.6%(12/157) Any AE: 80.9%(127/157) vs 72.6%(114/157) vs 86.6%(136/157) Arthralgia: 0.6%(1/157) vs 3.2%(5/157) vs 5.1%(8/157) Chills: 0.6%(1/157) vs 0.6%(1/157) vs 3.2%(5/157) Constipation: 8.3%(13/157) vs 4.5%(7/157) vs 12.7%(20/157) Cough: 3.2%(5/157) vs 1.3%(2/157) vs 3.2%(5/157) Deaths: 0.0%(0/157) vs 0.0%(0/157) vs 0.0%(0/157)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 3</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 471</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 223</p> <p>Method of AE assessment: Monitored</p>	<p>None</p> <p>Timing of outcome assessment: 14, 56, 70 days</p>	<p>Decreased Appetite: 3.2%(5/157) vs 1.9%(3/157) vs 2.5%(4/157)</p> <p>Diarrhea: 12.1%(19/157) vs 7.0%(11/157) vs 12.1%(19/157)</p> <p>Dizziness: 18.5%(29/157) vs 14.0%(22/157) vs 33.8%(53/157)</p> <p>Dry Mouth: 14.0%(22/157) vs 8.3%(13/157) vs 38.2%(60/157)</p> <p>Dyspepsia: 3.2%(5/157) vs 5.7%(9/157) vs 7.6%(12/157)</p> <p>Dyspnea: 0.6%(1/157) vs 2.5%(4/157) vs 3.2%(5/157)</p> <p>Extrapyramidal Disorder: 9.6%(15/157) vs 5.1%(8/157) vs 8.3%(13/157)</p> <p>Fatigue: 8.9%(14/157) vs 5.1%(8/157) vs 12.1%(19/157)</p> <p>Gastroenteritis: 0.6%(1/157) vs 3.2%(5/157) vs 1.9%(3/157)</p> <p>Headache: 31.2%(49/157) vs 31.2%(49/157) vs 26.1%(41/157)</p> <p>Hot Flush: 4.5%(7/157) vs 1.3%(2/157) vs 3.2%(5/157)</p> <p>Hyperhidrosis: 7.6%(12/157) vs 5.7%(9/157) vs 5.1%(8/157)</p> <p>Hypersomnia: 1.3%(2/157) vs 0.6%(1/157) vs 5.7%(9/157)</p> <p>Increased Appetite: 1.9%(3/157) vs 3.8%(6/157) vs 7.0%(11/157)</p> <p>Influenza: 1.9%(3/157) vs 2.5%(4/157) vs 5.1%(8/157)</p> <p>Insomnia: 14.6%(23/157) vs 14.0%(22/157) vs 14.0%(22/157)</p> <p>Irritability: 5.1%(8/157) vs 5.1%(8/157) vs 5.7%(9/157)</p> <p>Musculoskeletal Stiffness: 1.9%(3/157) vs 1.9%(3/157) vs 3.2%(5/157)</p> <p>Myalgia: 7.6%(12/157) vs 3.8%(6/157) vs 7.0%(11/157)</p> <p>Nasal Congestion: 0.0%(0/157) vs 0.6%(1/157) vs 2.5%(4/157)</p> <p>Nasopharyngitis: 4.5%(7/157) vs 5.7%(9/157) vs 1.3%(2/157)</p> <p>Nausea: 29.9%(47/157) vs 19.1%(30/157) vs 21.7%(34/157)</p> <p>Pain In Extremity: 3.8%(6/157) vs 0.6%(1/157) vs 1.9%(3/157)</p> <p>Palpitations: 5.1%(8/157) vs 3.8%(6/157) vs 3.8%(6/157)</p> <p>Paraesthesia: 2.5%(4/157) vs 1.3%(2/157) vs 2.5%(4/157)</p> <p>Rash: 0.6%(1/157) vs 0.0%(0/157) vs 3.2%(5/157)</p> <p>Restlessness: 1.9%(3/157) vs 0.6%(1/157) vs 2.5%(4/157)</p> <p>Sedation: 5.1%(8/157) vs 3.2%(5/157) vs 10.8%(17/157)</p> <p>Serious Ae Leading To Death: 0.0%(0/157) vs 0.0%(0/157) vs 0.0%(0/157)</p> <p>Serious Ae, All: 1.9%(3/157) vs 0.6%(1/157) vs 2.5%(4/157)</p> <p>Somnolence: 8.3%(13/157) vs 3.8%(6/157) vs 35.7%(56/157)</p> <p>Tachycardia: 0.6%(1/157) vs 0.6%(1/157) vs 4.5%(7/157)</p> <p>Thirst: 0.6%(1/157) vs 0.0%(0/157) vs 2.5%(4/157)</p> <p>Vision Blurred: 2.5%(4/157) vs 3.2%(5/157) vs 3.8%(6/157)</p> <p>Vomiting: 3.8%(6/157) vs 1.9%(3/157) vs 5.7%(9/157)</p> <p>Weight Increased: 1.3%(2/157) vs 0.0%(0/157) vs 3.8%(6/157)</p> <p>Withdrawals:</p> <p>Escitalopram vs Placebo vs Quetiapine</p> <p>Withdrawals:56.1%(88/157) vs 53.5%(84/157) vs 48.4%(76/157)</p> <p>Withdrawals Due To Adverse Events:7.0%(11/157) vs 4.5%(7/157) vs 15.9%(25/157)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Bortnick et al. 2011¹⁷⁰</p> <p>Depression</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Opal (D1448C00003)</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 4</p> <p>Age: Mean: 18</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 513 Eligible: 310 Entering: 310 Withdrawn: 68 Lost to follow-up: 23 Analyzed: 219</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Inclusion criteria: 18-65 years old, DSM-IV diagnosis of MDD. HAM-D total score \geq 22. HAM-D item I \geq 2</p> <p>Exclusion criteria: DSM-IV Axis I disorder other than MDD within 6 months. DSM-IV Axis II disorder major impact, substance abuse, HAM-D item 3 \geq 3, severe medical illness, ECG significant depression can be no longer than 12 months or less than 4 weeks.</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 50-300 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Wash-out: Psychotropics for 1-4 week(s) were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56, 70 days</p>	<p>Results: Depression: Change in MADRS (% Remitted) at 8 weeks: Quetiapine vs Placebo - RR = 1.39 (0.97 , 1.98)</p> <p>Depression: Change in MADRS (% Responder) at 8 weeks: Quetiapine vs Placebo - RR = 1.29 (1.05 , 1.59)</p> <p>Adverse Events: Excluded from analysis: Constipation: 1.3%(2/156) vs 5.2%(8/154) Dizziness: 3.2%(5/156) vs 7.1%(11/154) Dry Mouth: 6.4%(10/156) vs 32.5%(50/154) Fatigue: 0.0%(0/156) vs 6.5%(10/154) Headache: 10.3%(16/156) vs 10.4%(16/154) Increased Appetite: 1.3%(2/156) vs 6.5%(10/154) Increased Qtc Interval: 0.0%(0/156) vs 0.0%(0/154) Madr Item 10 (Suicidal Thoughts) Score =4: 0.6%(1/156) vs 2.6%(4/154) Nasal Congestion: 1.9%(3/156) vs 5.2%(8/154) Nasopharyngitis: 7.1%(11/156) vs 2.6%(4/154) Nausea: 5.8%(9/156) vs 4.5%(7/154) Patients Experiencing A =7% Increase In Weight: 1.3%(2/156) vs 2.6%(4/154) Sedation: 1.9%(3/156) vs 21.4%(33/154) Sedation Leading To Discontinuation: 0.6%(1/156) vs 3.9%(6/154) Somnolence: 5.1%(8/156) vs 20.1%(31/154) Somnolence Leading To Discontinuation: 0.0%(0/156) vs 2.6%(4/154) Quetiapine XR Clinically Relevant Differences in The Mean Change From Baseline To Week 8 In Vital Signs, Hematology, Ecgs Or Clinical Laboratory Parameters.: 0.0%(0/154)</p> <p>Withdrawals: Placebo vs Quetiapine XR Withdrawals: 28.8%(45/156) vs 29.9%(46/154) Withdrawals Due To Adverse Events: 2.6%(4/156) vs 8.4%(13/154)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Bissada et al. 2008¹⁸⁰</p> <p>Eating disorder</p> <p>Olanzapine</p> <p>Location: Canada</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 100% Female</p> <p>Race: Not reported</p> <p>Screened: 147 Eligible: 76 Entering: 34 Withdrawn: 6 Lost to follow-up: 0 Analyzed: 28</p> <p>Method of AE assessment: Not reported</p>	<p>Inclusion criteria: DSM-IV criteria for anorexia or nervosa (restricting or binge / purge subtype) including a body index <= 17.5 kg/m²</p> <p>Exclusion criteria: Active suicidal intent, comorbid substance abuse disorder, bipolar disorder, schizophrenia or any other psychotic disorder, organic brain syndromes or dissociative disorders, pregnancy, and failure to use contraception if sexually active</p> <p>Interventions: Placebo for 10 weeks vs Olanzapine 2.5-10 mg/days flexible dose for 10 weeks</p> <p>Run-in/wash-out period: Run-in: No drug for 2 week(s).</p> <p>Comorbidities: Anxiety</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Results: Eating Disorder: Change in BMI (BMI) at 4 weeks: Olanzapine vs Placebo - WMD = 0.11 (-0.77 , 0.99)</p> <p>Eating Disorder: Change in BMI (BMI) at 12 weeks: Olanzapine vs Placebo - WMD = 0.15 (-0.80 , 1.10)</p> <p>Adverse Events: Olanzapine vs Placebo De Novo Development Of Diabetes Mellitus: 0.0%(0/16) vs 0.0%(0/18) Evidence Of Impaired Glucose Tolerance: 0.0%(0/16) vs 0.0%(0/18) Serious Adverse Events (Extrapyramidal Symptoms, Excessive Sleepiness, Dizziness Or Galactorrhea): 0.0%(0/16) vs 0.0%(0/18)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:12.5%(2/16) vs 22.2%(4/18)</p>
<p>Brambilla et al. 2007¹⁸²</p> <p>Eating disorder</p> <p>Olanzapine</p>	<p>Inclusion criteria: Anorexia nervosa per DSM-IV restricted or binge-purging type</p> <p>Exclusion criteria: General medical impairments, endocrine,</p>	<p>Results: Eating Disorder: Change in BMI (BMI) at 4 weeks: Olanzapine vs Placebo - WMD = -0.00 (-0.91 , 0.91)</p> <p>Eating Disorder: Change in BMI (BMI) at 12 weeks: Olanzapine vs Placebo - WMD = 0.60 (-0.55 , 1.75)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: 100% Female</p> <p>Race: Not reported</p> <p>Screened: 35 Eligible: 30 Entering: NR Withdrawn: 5 Lost to follow-up: 0 Analyzed: 30</p> <p>Method of AE assessment: Not reported</p>	<p>metabolic and immune alterations (other than those limited to anorexia nervosa), cerebral trauma, epilepsy</p> <p>Interventions: Placebo for 3 months vs Olanzapine 2.5-5 mg/days fixed titration schedule for 3 months</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression, OCD, Personality Disorder</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	
<p>Brambilla et al. 2007¹⁸³</p> <p>Eating disorder</p> <p>Olanzapine</p> <p>Location: Not reported</p> <p>Trial: Not reported</p> <p>Funding source:</p>	<p>Inclusion criteria: Anorexia nervosa according to DSM-IV</p> <p>Exclusion criteria: General medical, neuroendocrine, metabolic, immunologic alterations other than these related to AN, axis I and II psychopathologies other than AN. Axis I and II psychopathologies other than AN</p> <p>Interventions:</p>	<p>Results: Eating Disorder: Change in BMI (BMI) at 4 weeks: Olanzapine vs Placebo - WMD = -0.20 (-1.44 , 1.04)</p> <p>Eating Disorder: Change in BMI (BMI) at 12 weeks: Olanzapine vs Placebo - WMD = 0.20 (-1.05 , 1.45)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Hospital</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: 100% Female</p> <p>Race: Not reported</p> <p>Screened: 20 Eligible: 20 Entering: 20 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Not reported</p>	<p>Placebo for 3 months vs Olanzapine 2.5-5 mg/days fixed titration schedule for 3 months</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 30, 61, 91 days</p>	
<p>Gaskill et al. 2001¹⁸⁴</p> <p>Eating disorder</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: CCT only</p> <p>Setting: Single setting</p>	<p>Inclusion criteria: Not reported</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Control Group vs Olanzapine 1.25-15 mg/days flexible dose for duration not reported</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p>	<p>Results: Eating Disorder: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 0</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: 46</p> <p>Method of AE assessment: Not reported</p>	<p>Timing of outcome assessment: days</p>	
<p>Court et al. 2010¹⁸⁵</p> <p>Eating disorder</p> <p>Quetiapine</p> <p>Location: Australia/New Zealand</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 80-99% Female</p>	<p>Inclusion criteria: Diagnosis of AN per DSM-IV, no previous antipsychotic for > 1 week</p> <p>Exclusion criteria: Atypical antipsychotic >= 7 days, psychotic illness, history of brain infarct or brain surgery, diabetes, IQ < 70</p> <p>Interventions: Other, Treatment as usual 998 Not reported/Not reported frequency not reported for 12 weeks vs Quetiapine 322.5 150-500 mg/days fixed titration schedule for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression</p>	<p>Results: Eating Disorder: Change in BMI at 12 weeks: Quetiapine vs TAU - WMD = -0.10 (-1.74 , 1.54)</p> <p>Adverse Events: Quetiapine vs Usual tx Admitted As An Inpatient At A Hospital: 46.7%(7/15) vs 44.4%(8/18)</p> <p>Withdrawals: Quetiapine vs Usual tx Withdrawals:33.3%(5/15) vs 38.9%(7/18) Withdrawals Due To Adverse Events:13.3%(2/15) vs 0.0%(0/18)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Not reported</p> <p>Screened: NR Eligible: 33 Entering: 33 Withdrawn: 12 Lost to follow-up: 0 Analyzed: 21</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 182, 364 days</p>	
<p>Tassniyom et al. 2010³⁰⁷</p> <p>Insomnia</p> <p>Quetiapine</p> <p>Location: Asia</p> <p>Trial: Not reported</p> <p>Funding source: Faculty of Medicine Khon Kean University</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 4</p> <p>Age: Mean: 25</p> <p>Sex: 80-99% Female</p> <p>Race: Not reported</p>	<p>Inclusion criteria: 16-65, primary insomnia per DSM-IV-TR</p> <p>Exclusion criteria: Other psychiatric diagnosis, receiving sedating meds, medical diseases, pregnant, unable to record sleep log, answer questionnaires, or refused</p> <p>Interventions: Placebo 25 mg/days fixed single dose for 2 weeks vs Quetiapine 25 mg/days fixed single dose for 2 weeks</p> <p>Run-in/wash-out period: Run-in: Psychotropics for 1 week(s). Patients who met the study criteria were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14 days</p>	<p>Results: Insomnia: Change in SL at 2 weeks: Quetiapine vs Placebo - WMD = -72.43 (-155.52 , 10.66)</p> <p>Insomnia: Change in Sleep Satisfaction at 2 weeks: Quetiapine vs Placebo - WMD = 5.70 (-16.95 , 28.35)</p> <p>Insomnia: Change in TST at 2 weeks: Quetiapine vs Placebo - WMD = 52.68 (-58.13 , 163.49)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Monitored		
<p>Rothbaum et al. 2008²³⁷ PTSD Risperidone Location: US Trial: Not reported Funding source: Industry Design: RCT only Setting: Multi-center Jadad: 4 Age: Not reported Sex: 80-99% Female Race: Caucasian, African Ancestry, Other-NOS Screened: 91 Eligible: 25 Entering: 25 Withdrawn: 5 Lost to follow-up: 0 Analyzed: 20 Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-65, PTSD due to civilian trauma, CAPS >=50</p> <p>Exclusion criteria: Combat related events</p> <p>Interventions: Placebo for 8 weeks vs Risperidone 0.5-3 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Run-in: Sertraline for 8 week(s). Non-responders were randomized.</p> <p>Comorbidities: Anxiety, Depression</p> <p>Timing of outcome assessment: 56, 63, 70, 84, 98, 112 days</p>	<p>Results: PTSD: Change in CAPS at 8 weeks: Risperidone vs Placebo - WMD = 4.08 (-10.17 , 18.34)</p> <p>PTSD: Change in CAPS at 16 weeks: Risperidone vs Placebo - WMD = -2.35 (-18.69 , 13.99)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:0.0%(0/11) vs 35.7%(5/14) Withdrawals Due To Adverse Events:0.0%(0/11) vs 28.6%(4/14) Withdrawals Due To Adverse Events Of Elevated Liver Enzyme Levels:0.0%(0/11) vs 7.1%(1/14) Withdrawals Due To Adverse Events Of Probable Dystonic Reaction Before Given Drug:0.0%(0/11) vs 7.1%(1/14) Withdrawals Due To Adverse Events Of Tachycardia:0.0%(0/11) vs 7.1%(1/14) Withdrawals Due To Adverse Events Of Visiting ER Twice With Unremitting Chest Pain:0.0%(0/11) vs 7.1%(1/14)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Hamner et al. 2009²³⁹</p> <p>PTSD</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: 18-65 years old, DSM-IV diagnosis of PTSD, CAPS symptom status version >=50</p> <p>Exclusion criteria: A history of sensitivity to quetiapine, substance abuse, schizophrenia, schizoaffective disorder, bipolar disorder, dementia</p> <p>Interventions: Placebo for 12 weeks vs Quetiapine 258 (25-800) mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Wash-out: Placebo for 1 week(s) were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 84 days</p>	<p>Results: PTSD: Insufficient data to calculate an effect size</p>
<p>Nickel et al. 2007²¹⁹</p> <p>Personality disorder</p> <p>Aripiprazole</p> <p>Location: Western</p>	<p>Inclusion criteria: Same as ID 2754</p> <p>Exclusion criteria: Schizophrenia, current use of psychotic medication in previous placebo group, termination of aripiprazole, current</p>	<p>Results: Personality Disorder: Change in SCL-90 (GSI) at 72 weeks: Aripiprazole vs Placebo - WMD = -16.50 (-20.51 , -12.49)</p> <p>Adverse Events: Aripiprazole vs Placebo Anxiety: 15.4%(4/26) vs 19.2%(5/26)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not funded</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 2</p> <p>Age: Mean: 22</p> <p>Sex: 80-99% Female</p> <p>Race: Not reported</p> <p>Screened: 52 Eligible: 52 Entering: 52 Withdrawn: 13 Lost to follow-up: 0 Analyzed: 39</p> <p>Method of AE assessment: Not reported</p>	<p>psychotherapy, pregnancy, suicide ideation, severe somatic illness, substance abuse</p> <p>Interventions: Placebo for 18 months vs Aripiprazole 15 mg/days fixed single dose for 18 months</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression, OCD</p> <p>Timing of outcome assessment: 182, 365, 547 days</p>	<p>Constipation: 15.4%(4/26) vs 11.5%(3/26) Headache: 34.6%(9/26) vs 30.8%(8/26) Insomnia: 30.8%(8/26) vs 23.1%(6/26) Nausea: 15.4%(4/26) vs 15.4%(4/26) Numbness: 11.5%(3/26) vs 3.8%(1/26) Restlessness: 11.5%(3/26) vs 7.7%(2/26) Significant Weight Change: 0.0%(0/26) vs 0.0%(0/26)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:15.4%(4/26) vs 34.6%(9/26)</p>
<p>Pascual et al. 2008²²²</p> <p>Personality disorder</p> <p>Ziprasidone</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source:</p>	<p>Inclusion criteria: Borderline personality disorder, 18-45, CGI-5 >= 4, contraception in females</p> <p>Exclusion criteria: Comorbidity, schizophrenia, drug-induced psychosis, organic brain syndrome, alcohol or other substance dependence, bipolar, mental retardation, major depressive episode</p> <p>Interventions: Placebo for 12 weeks</p>	<p>Results: Personality Disorder: Change in SCL-90-R (GSI) at 14 weeks: Ziprasidone vs Placebo - WMD = 0.18 (-0.35 , 0.71)</p> <p>Adverse Events: Placebo vs Ziprasidone Dizziness: 0.0%(0/30) vs 13.3%(4/30) Gastrointestinal Symptoms: 6.7%(2/30) vs 0.0%(0/30) Headache: 3.3%(1/30) vs 0.0%(0/30) Hyperprolactinemia Not Clinically Relevant: 0.0%(0/30) vs 6.7%(2/30) Minor Sedation: 3.3%(1/30) vs 20.0%(6/30) Movement Disorders, Dystonia, Akathisia, Rigidity Or Hyperkinesia: 0.0%(0/30) vs</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Government, Industry, REM-TAP Network</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 80-99% Female</p> <p>Race: Not reported</p> <p>Screened: 127 Eligible: 65 Entering: 60 Withdrawn: NR Lost to follow-up: NR Analyzed: 29</p> <p>Method of AE assessment: Monitored</p>	<p>vs Ziprasidone 40-200 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 42, 56, 70, 84 days</p>	<p>0.0%(0/30) Serious Adverse Events: 0.0%(0/30) vs 0.0%(0/30) Significant Changes In Weight Or Blood Pressure: 0.0%(0/30) vs 0.0%(0/30) Treatment-Emergent Adverse Events: 13.3%(4/30) vs 36.7%(11/30) Uneasy Feeling: 0.0%(0/30) vs 10.0%(3/30)</p> <p>Withdrawals: Placebo vs Ziprasidone Withdrawals:46.7%(14/30) vs 56.7%(17/30) Withdrawals Due To Adverse Events:0.0%(0/30) vs 30.0%(9/30) Withdrawals Due To Adverse Events Of Needed Psychiatric Hospitalization:10.0%(3/30) vs 13.3%(4/30) Withdrawals Due To Treatment-Emergent Adverse Events:0.0%(0/30) vs 13.3%(4/30)</p>
<p>McClure et al. 2009²²⁷</p> <p>Personality disorder</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p>	<p>Inclusion criteria: 18-60, schizotypal personality disorder</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 10 weeks vs Risperidone 0.25-2 mg/days fixed titration schedule for 10 weeks</p> <p>Run-in/wash-out period: Run-in: Placebo for 2 week(s). Symptomatically stable patients were randomized.</p>	<p>Results: Personality Disorder: Change in PANSS (negative) at 12 weeks: Risperidone vs Placebo - WMD = -1.00 (-6.50 , 4.50)</p> <p>Personality Disorder: Change in PANSS (postive) at 12 weeks: Risperidone vs Placebo - WMD = -1.70 (-5.80 , 2.40)</p> <p>Personality Disorder: Change in PANSS (general) at 12 weeks: Risperidone vs Placebo - WMD = -1.80 (-9.68 , 6.08)</p> <p>Withdrawals: Placebo vs Risperidone Galactorrhea (Leading To Withdrawal):0.0%(0/12) vs 5.3%(1/19) Increase In Suicidal Ideation (Leading To Withdrawal):0.0%(0/12) vs 5.3%(1/19) Withdrawals:25.0%(3/12) vs 42.1%(8/19) Risperidone Withdrawals Due To Adverse Events:10.5%(2/19)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: 31</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 20</p> <p>Method of AE assessment: Not reported</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 42, 84 days</p>	
<p>Schulz et al. 2008²²³</p> <p>Personality disorder</p> <p>Olanzapine</p> <p>Location: US, UK, Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p>	<p>Inclusion criteria: 18-65, DSM-IV for personality disorder and DSM-IV for borderline personality disorder by DIPD-IV, ZAN-BPD = q at randomization</p> <p>Exclusion criteria: Schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I, delusional disorder by DSM-IV Axis I, major depressive disorder, bipolar II, substance dependence within 3 month, actively suicidal PTSD, panic disorder, OCD BMI < 17, cluster A personality disorder.</p> <p>Interventions: Placebo for 12 weeks vs Olanzapine 2.5-20 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p>	<p>Results: Personality Disorder: Change in SCL-90-R (GSI) at 12 weeks: Olanzapine vs Placebo - WMD = -0.04 (-0.31 , 0.23)</p> <p>Adverse Events: Olanzapine vs Placebo Aggression: 0.6%(1/155) vs 1.3%(2/159) Agitation: 0.6%(1/155) vs 0.0%(0/159) Alcoholism: 0.6%(1/155) vs 0.0%(0/159) Anxiety: 4.5%(7/155) vs 5.0%(8/159) Appetite Increased: 17.4%(27/155) vs 7.5%(12/159) Deaths During Study: 0.0%(0/155) vs 0.0%(0/159) Depressed Mood: 0.0%(0/155) vs 0.6%(1/159) Drug Misuse: 0.6%(1/155) vs 0.0%(0/159) Dry Mouth: 7.1%(11/155) vs 3.8%(6/159) Exacerbation Of Borderline Personality Disorder Symptoms: 0.0%(0/155) vs 1.3%(2/159) Fatigue: 10.3%(16/155) vs 7.5%(12/159) Headache: 14.8%(23/155) vs 11.3%(18/159) Impulsive Behavior: 0.6%(1/155) vs 0.0%(0/159) Incidence Of Treatment-Emergent Abnormal High Levels Of Prolactin At Endpoint: 19.4%(30/155) vs 8.8%(14/159) Insomnia: 2.6%(4/155) vs 6.3%(10/159)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Caucasian, Other-NOS</p> <p>Screened: 385 Eligible: 314 Entering: 314 Withdrawn: 119 Lost to follow-up: 17 Analyzed: 175</p> <p>Method of AE assessment: Monitored</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56, 70, 84 days</p>	<p>Nausea: 4.5%(7/155) vs 7.5%(12/159) Participants With >=1 Treatment-Emergent Adverse Event: 65.8%(102/155) vs 56.6%(90/159) Sedation: 11.6%(18/155) vs 1.3%(2/159) Self-Injurious Ideation: 0.6%(1/155) vs 0.0%(0/159) Self-Mutilation: 0.6%(1/155) vs 0.0%(0/159) Serious AE: 3.9%(6/155) vs 5.7%(9/159) Somnolence: 12.9%(20/155) vs 4.4%(7/159) Suicidal Ideation: 5.8%(9/155) vs 2.5%(4/159) Treatment-Emergent Weight Gain =7% Of Baseline: 32.9%(51/155) vs 2.5%(4/159) Weight Decrease: 0.0%(0/155) vs 0.6%(1/159) Weight Increased: 17.4%(27/155) vs 2.5%(4/159)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:48.4%(75/155) vs 38.4%(61/159) Withdrawals Due To Adverse Events:11.0%(17/155) vs 11.3%(18/159)</p>
<p>Linehan et al. 2008²²⁴</p> <p>Personality disorder</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 100% Female</p> <p>Race: Caucasian,</p>	<p>Inclusion criteria: Borderline, personality disorder according to personality disorder and conducted clinical interview for DSM-IV (SCID-II), borderline personality disorder for inappropriate anger on the SCID II, OAS-M irritability subscale >=6.</p> <p>Exclusion criteria: Schizophrenia, bipolar I, schizoaffective disorder, major depressive disorder with psychotic features or other psychotic disorder, mental or seizure disorder, substance dependence in the past 6 month according to DSM-IV, self-inflicted injury in the 8 weeks prior, pregnant, breast feeding or planning to be pregnant.</p> <p>Interventions: Placebo 2.5-15 mg/days flexible dose for duration not reported vs Olanzapine 2.5-15 mg/days flexible dose for duration not reported</p>	<p>Results: Personality Disorder: Insufficient data to calculate an effect size</p> <p>Adverse Events: Olanzapine vs Placebo Dizziness: 133.3%(16/12) vs 66.7%(8/12) Muscle Stiffness: 166.7%(20/12) vs 83.3%(10/12) Severe Nervousness: 0.0%(0/12) vs 83.3%(10/12) Sexual Dysfunction: 66.7%(8/12) vs 0.0%(0/12) Significantly Distressing Or Incapacitating Sedation: 83.3%(10/12) vs 16.7%(2/12) Weight Gain: 183.3%(22/12) vs 116.7%(14/12)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:33.3%(4/12) vs 33.3%(4/12)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>African Ancestry, Hispanic, Native American, Other-NOS</p> <p>Screened: 44 Eligible: 24 Entering: 24 Withdrawn: 8 Lost to follow-up: 0 Analyzed: 16</p> <p>Method of AE assessment: Not reported</p>	<p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression, Personality Disorder, Substance Abuse, Eating Disorder</p> <p>Timing of outcome assessment: 49, 98, 147 days</p>	
<p>van den Broek et al. 2008²²¹</p> <p>Personality disorder</p> <p>Quetiapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex:</p> <p>Race: Not reported</p>	<p>Inclusion criteria: DSM-IV diagnosis of borderline personality disorder</p> <p>Exclusion criteria: Schizophrenia, current major depression, bipolar disorder, substance dependence</p> <p>Interventions: Placebo for 8 weeks vs Quetiapine 200-600 mg/days flexible dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 28, 42, 56, 70 days</p>	<p>Results: Personality Disorder: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p> Screened: NR Eligible: NR Entering: 24 Withdrawn: 8 Lost to follow-up: NR Analyzed: 16 Method of AE assessment: Not reported </p>		
<p> Zanarini et al. 2007²²⁰ Personality disorder Olanzapine Location: Not reported Trial: Not reported Funding source: Not reported Design: RCT only Setting: Not reported Jadad: 2 Age: Not reported Sex: Race: Not reported Screened: NR Eligible: NR Entering: 451 Withdrawn: NR Lost to follow-up: NR Analyzed: NR </p>	<p> Inclusion criteria: 18-65 years old, diagnosis of DSM-IV BPD Exclusion criteria: Not reported Interventions: Placebo for 12 weeks vs Olanzapine 2.5 mg/days frequency not reported for 12 weeks vs Olanzapine 5-10 mg/days frequency not reported for 12 weeks Run-in/wash-out period: Not reported Comorbidities: None Timing of outcome assessment: 84 days </p>	<p> Results: Personality Disorder: Change in Zanarini Rating Scale (Response Rate) at 12 weeks: Olanzapine 2.5mg/d vs Placebo - RR = 1.04 (0.86 , 1.26) Personality Disorder: Change in Zanarini Rating Scale (Response Rate) at 12 weeks: Olanzapine 5-10mg/d vs Placebo - RR = 1.28 (1.08 , 1.51) </p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Method of AE assessment: Not reported</p>		
<p>Kampman et al. 2007²⁵⁹</p> <p>Substance abuse</p> <p>Quetiapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Mean: 47</p> <p>Sex: Mixed</p> <p>Race: Caucasian, Other-NOS</p> <p>Screened: 87 Eligible: 72 Entering: 61 Withdrawn: 5 Lost to follow-up: 6 Analyzed: 61</p> <p>Method of AE assessment: Monitored, elicited by investigator</p>	<p>Inclusion criteria: Aged \geq 18 years old, alcohol dependence, have a consecutive 30 days period drinking at least 48 standard drinks, \geq 2 days of heavy drinking, \geq 3 consecutive days of abstinence, Clinical Institutes Withdrawal Assessment for Alcohol score $<$ 8.</p> <p>Exclusion criteria: Diagnosis of any psychoactive substance dependence other than alcohol or nicotine, current use of psychoactive drugs, taking psychotropic medications, current, severe psychiatric symptoms, severe medical illness, history of seizures or severe head trauma.</p> <p>Interventions: Placebo 50-400 mg/days fixed titration schedule for 12 weeks vs Quetiapine 50-400 mg/days fixed titration schedule for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression, OCD, Personality Disorder, PTSD</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Results: Substance Abuse: Change in Complete Abstinence (Alcohol) at 12 weeks: Quetiapine vs Placebo - RR = 4.97 (1.17 , 21.11)</p> <p>Adverse Events: Quetiapine vs Placebo Aches And Pains: 44.8%(13/29) vs 56.3%(18/32) Dry Mouth: 31.0%(9/29) vs 0.0%(0/32) Dysphoria: 31.0%(9/29) vs 21.9%(7/32) Gastrointestinal Complaints: 41.4%(12/29) vs 37.5%(12/32) Headache: 27.6%(8/29) vs 28.1%(9/32) Insomnia: 3.4%(1/29) vs 18.8%(6/32) Lightheaded: 17.2%(5/29) vs 12.5%(4/32) Sedation: 51.7%(15/29) vs 18.8%(6/32) Skin Rash: 10.3%(3/29) vs 3.1%(1/32) Upper Respiratory Tract Infection: 37.9%(11/29) vs 31.3%(10/32)</p> <p>Withdrawals: Quetiapine vs Placebo Withdrawals:20.7%(6/29) vs 25.0%(8/32) Withdrawals Due To Adverse Events:0.0%(0/29) vs 3.1%(1/32)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Loebl et al. 2008²⁶⁹</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: 100% Male</p> <p>Race: Caucasian, African Ancestry</p> <p>Screened: 89 Eligible: 31 Entering: 31 Withdrawn: NR Lost to follow-up: NR Analyzed: 14</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Men, 18-60, cocaine dependence, using cocaine ≥ 1 every other week</p> <p>Exclusion criteria: Schizophrenia, bipolar disorder, MDD, HIV, head trauma with loss of consciousness, unstable medical condition</p> <p>Interventions: Placebo for 12 weeks vs Risperidone 1-2 mg pills daily fixed titration schedule and 25mg injection biweekly fixed dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Anxiety, Depression, Substance Abuse</p> <p>Timing of outcome assessment: 7, 14, 21, 35, 49, 63, 77 days</p>	<p>Results: Substance Abuse: Change in ASI (Drug Composite) at 12 weeks: Risperidone vs Placebo - WMD = -0.03 (-0.09 , 0.03)</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:60.0%(9/15) vs 50.0%(8/16) Withdrawals Due To Adverse Events:0.0%(0/15) vs 12.5%(2/16)</p>
<p>Anton et al. 2008²⁵²</p> <p>Substance abuse</p> <p>Aripiprazole</p>	<p>Inclusion criteria: 21-65 years old, alcohol dependence, presents at 3 visits with negative breathalyzer results and abstain from alcohol before randomization score < 8 on Clinical Institute Withdrawal Assessment for Alcohol Revised</p>	<p>Results: Substance Abuse: Change in Complete Abstinence (Alcohol) at 12 weeks: Aripiprazole vs Placebo - RR = 0.50 (0.29 , 0.88)</p> <p>Substance Abuse: Change in Abstinent Days (Alcohol) at 12 weeks: Aripiprazole vs Placebo - SMD = -0.13 (-0.36 , 0.10)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 47</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Asian/Pacific Islander, Other-NOS</p> <p>Screened: 691 Eligible: 295 Entering: 295 Withdrawn: 75 Lost to follow-up: 25 Analyzed: 195</p> <p>Method of AE assessment: Monitored</p>	<p>Exclusion criteria: Substance abuse on drugs other than cocaine and opiates with exception of marijuana abuse within past year, pregnant, axis I or II disorder, high suicidal risk, allergy to aripiprazole taking an investigational agent within past month.</p> <p>Interventions: Placebo 27.4 mg/days average final dose for 12 weeks vs Aripiprazole 2-30 mg/days fixed titration schedule for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 28, 56, 84 days</p>	<p>Adverse Events: Aripiprazole vs Placebo Anxiety: 12.8%(19/149) vs 2.7%(4/146) Clinically Significant Alt Elevations (Alt [sgpt]=3x Upper Limit Of Normal): 3.4%(5/149) vs 0.0%(0/146) Clinically Significant Ast Elevations (Ast [sgot]=3x Upper Limit Of Normal): 2.7%(4/149) vs 1.4%(2/146) Death: 0.0%(0/149) vs 0.0%(0/146) Diarrhea: 6.7%(10/149) vs 5.5%(8/146) Disturbance In Attention: 9.4%(14/149) vs 2.1%(3/146) Dizziness: 7.4%(11/149) vs 7.5%(11/146) EPS-Related AE: Akathisia: 6.0%(9/149) vs 0.7%(1/146) EPS-Related AE: Dyskinesia: 1.3%(2/149) vs 0.0%(0/146) EPS-Related AE: Tremor: 3.4%(5/149) vs 2.7%(4/146) EPS-Related AEs: 9.4%(14/149) vs 3.4%(5/146) Fatigue: 24.2%(36/149) vs 6.8%(10/146) Headache: 20.1%(30/149) vs 24.0%(35/146) Increased Appetite: 5.4%(8/149) vs 2.7%(4/146) Insomnia: 21.5%(32/149) vs 11.0%(16/146) Nausea: 6.7%(10/149) vs 6.8%(10/146) Restlessness: 18.1%(27/149) vs 2.7%(4/146) Serious AE: 2.7%(4/149) vs 2.7%(4/146) Serious AE: Accidental Overdose: 0.0%(0/149) vs 0.7%(1/146) Serious AE: Atrial Fibrillation: 0.0%(0/149) vs 0.7%(1/146) Serious AE: Cellulitis: 0.7%(1/149) vs 0.0%(0/146) Serious AE: Chest Pain: 0.7%(1/149) vs 0.0%(0/146) Serious AE: Migraine: 0.7%(1/149) vs 0.0%(0/146) Serious AE: Overdose (Not Accidental): 0.0%(0/149) vs 0.7%(1/146) Serious AE: Thrombosis: 0.7%(1/149) vs 0.0%(0/146) Serious AE: Worsening Alcoholism: 0.0%(0/149) vs 0.7%(1/146) Somnolence: 16.8%(25/149) vs 5.5%(8/146) Treatment Related AE: 81.2%(121/149) vs 61.6%(90/146) Used Anticholinergic For Potential EPS: 2.7%(4/149) vs 0.0%(0/146)</p> <p>Withdrawals: Aripiprazole Anxiety Leading To Withdrawal:3.4%(5/149) Insomnia Leading To Withdrawal:6.7%(10/149) Restlessness Leading To Withdrawal:2.7%(4/149) Aripiprazole vs Placebo Withdrawals:40.9%(61/149) vs 26.7%(39/146) Withdrawals Due To Adverse Events:14.1%(21/149) vs 0.7%(1/146)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Grabowski et al.2000²⁶⁶</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: 193</p> <p>Eligible: NR</p> <p>Entering: NR</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Not reported</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 12 weeks vs Risperidone 2 mg/days fixed single dose for 12 weeks vs Risperidone 4 mg/days fixed single dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p>
<p>Grabowski et al. 2004²⁷⁴</p> <p>Substance abuse</p> <p>Risperidone</p>	<p>Inclusion criteria: 18-50, dual dependent (cocaine and heroin) good medical health, without other psych diagnosis (except nicotine dependence)</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Placebo vs Risperidone 2mg vs Risperidone 4mg</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: 120 Eligible: NR Entering: 96 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 26 weeks vs Risperidone 2 mg/days frequency not reported for 26 weeks vs Risperidone 4 mg/days frequency not reported for 26 weeks</p> <p>Run-in/wash-out period: Wash-out: Risperidone stabilization for 2 weeks. Patients in symptomatic remission were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 days</p>	<p>Withdrawals:78.8%(26/33) vs 65.6%(21/32) vs 54.8%(17/31)</p>
<p>Guardia et al. 2004²⁵⁶</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: DSM-IV for alcohol dependence disorder age 18 - 60</p> <p>Exclusion criteria: Pregnancy, breast feeding, severe organic disorder, AST or ALT > 150 units /l, severe psychiatric disorders or psychotic disorders, bipolar I, severe major depressive disorder with suicidal risk, severe personality disorder,</p>	<p>Results: Substance Abuse: Change in Abstinent Days (Alcohol) at 12 weeks: Olanzapine vs Placebo - SMD = -0.35 (-0.86 , 0.16)</p> <p>Adverse Events: Olanzapine vs Placebo Amenorrhea: 3.4%(1/29) vs 3.2%(1/31) Anxiety: 3.4%(1/29) vs 12.9%(4/31) Appetite Increase: 24.1%(7/29) vs 9.7%(3/31) Constipation: 10.3%(3/29) vs 9.7%(3/31)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 5</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 60</p> <p>Entering: 60</p> <p>Withdrawn: 19</p> <p>Lost to follow-up: 0</p> <p>Analyzed: 41</p> <p>Method of AE assessment: Monitored</p>	<p>other current substance abuse or dependence disorder (except for nicotine) that was not in sustained remission, and less than 5 or more than 30 days since the last drink.</p> <p>Interventions: Placebo for 12 weeks vs Olanzapine 5-15 mg/days flexible dose for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56, 70, 84 days</p>	<p>Decreased Sexual Desire: 3.4%(1/29) vs 12.9%(4/31)</p> <p>Delayed Ejaculation: 3.4%(1/29) vs 6.5%(2/31)</p> <p>Depression: 6.9%(2/29) vs 9.7%(3/31)</p> <p>Dizziness: 0.0%(0/29) vs 9.7%(3/31)</p> <p>Drowsiness: 17.2%(5/29) vs 16.1%(5/31)</p> <p>Dry Mouth: 10.3%(3/29) vs 6.5%(2/31)</p> <p>Erection Difficulty: 3.4%(1/29) vs 6.5%(2/31)</p> <p>Hypokinesia: 3.4%(1/29) vs 3.2%(1/31)</p> <p>Itching: 3.4%(1/29) vs 0.0%(0/31)</p> <p>Loss Of Energy: 6.9%(2/29) vs 12.9%(4/31)</p> <p>Motor Tension: 0.0%(0/29) vs 9.7%(3/31)</p> <p>Muscle Stiffness: 3.4%(1/29) vs 0.0%(0/31)</p> <p>Orthostatic Hypotension: 3.4%(1/29) vs 12.9%(4/31)</p> <p>Photosensitivity: 6.9%(2/29) vs 3.2%(1/31)</p> <p>Tremor: 3.4%(1/29) vs 3.2%(1/31)</p> <p>Weight Gain: 31.0%(9/29) vs 12.9%(4/31)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:41.4%(12/29) vs 22.6%(7/31) Withdrawals Due To Adverse Events:0.0%(0/29) vs 3.2%(1/31)</p>
<p>Hamilton et al. 2009²⁶³</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p>	<p>Inclusion criteria: Age >= 18, cocaine dependence according to DSM-V, active use of cocaine within 30 days by urine test or self-report</p> <p>Exclusion criteria: Currently receiving antipsychotic medication, current DSM - IV diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder. current active psychotic symptoms, hallucinations, remarkably disorganized speech, history of bipolar disorder, major depressive disorder by hypersensitivity to olanzapine serious unstable medical illness.</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Adverse Events: Olanzapine vs Placebo</p> <p>Abdominal Pain: 13.0%(3/23) vs 20.0%(5/25)</p> <p>Akathisia: 39.1%(9/23) vs 28.0%(7/25)</p> <p>Amnesia: 21.7%(5/23) vs 4.0%(1/25)</p> <p>Any Side Effect: 100.0%(23/23) vs 96.0%(24/25)</p> <p>Articulation Impairment: 17.4%(4/23) vs 20.0%(5/25)</p> <p>Asthenia: 26.1%(6/23) vs 16.0%(4/25)</p> <p>Blepharitis: 8.7%(2/23) vs 4.0%(1/25)</p> <p>Chest Pain: 8.7%(2/23) vs 28.0%(7/25)</p> <p>Constipation: 26.1%(6/23) vs 40.0%(10/25)</p> <p>Dizziness: 21.7%(5/23) vs 16.0%(4/25)</p> <p>Dry Mouth: 69.6%(16/23) vs 44.0%(11/25)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Jadad: 4</p> <p>Age: Mean: 33</p> <p>Sex: 100% Male</p> <p>Race: Caucasian, African Ancestry</p> <p>Screened: NR</p> <p>Eligible: 48</p> <p>Entering: 52</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Interventions: Placebo 2.5-20 mg/days flexible dose for 16 weeks vs Olanzapine 2.5-20 mg/days flexible dose for 16 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: Depression, OCD, PTSD</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 42, 56, 70, 84 days</p>	<p>Euphoria: 13.0%(3/23) vs 12.0%(3/25) Increased Appetite: 87.0%(20/23) vs 60.0%(15/25) Muscle Twitching: 30.4%(7/23) vs 28.0%(7/25) Neck Rigidity: 26.1%(6/23) vs 28.0%(7/25) Non-Aggressive Behavior Changes: 26.1%(6/23) vs 28.0%(7/25) Peripheral Edema: 8.7%(2/23) vs 4.0%(1/25) Postural Hypotension: 52.2%(12/23) vs 28.0%(7/25) Rash: 8.7%(2/23) vs 4.0%(1/25) Somnolence: 73.9%(17/23) vs 56.0%(14/25) Stuttering: 17.4%(4/23) vs 20.0%(5/25) Tachycardia: 8.7%(2/23) vs 20.0%(5/25) Tremor: 17.4%(4/23) vs 20.0%(5/25) Weight Gain: 69.6%(16/23) vs 64.0%(16/25)</p>
<p>Hutchison et al. 2006²⁵⁷</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex: Mixed</p>	<p>Inclusion criteria: Excellent health - DSM - IV for alcohol dependence</p> <p>Exclusion criteria: Psychiatric diagnosis (bipolar disorder, schizophrenia, bulimia, anorexia nervosa) psychological disorder, recurring pharmacotherapy, endorsed current use of illicit drugs other than marijuana, or tested positive for the use of illicit drugs</p> <p>Interventions: Placebo 2.5-5 mg/days fixed single dose for 12 weeks vs Olanzapine 2.5-5 mg/days fixed titration schedule for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals: 18.2%(6/33) vs 22.6%(7/31)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Caucasian</p> <p>Screened: 154 Eligible: 78 Entering: 64 Withdrawn: 13 Lost to follow-up: 0 Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Comorbidities: None</p> <p>Timing of outcome assessment: 14, 28, 56, 84 days</p>	
<p>Kampman et al. 2003²⁶⁴</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting</p> <p>Jadad: 4</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Native American</p> <p>Screened: NR Eligible: NR</p>	<p>Inclusion criteria: \$100 worth of cocaine use in prior month, age 18-60 cocaine dependency</p> <p>Exclusion criteria: Substance dependency besides nicotine and alcohol, severe alcohol dependence, psychosis, dementia, use of other psychotropic medications, unstable medical illness, history of hypersensitivity to olanzapine</p> <p>Interventions: Placebo 2.5-10 mg/days fixed titration schedule for 11 weeks vs Olanzapine 2.5-10 mg/days fixed titration schedule for 11 weeks</p> <p>Run-in/wash-out period: Run-in: Psychosocial treatment for 1 week(s). Eligible participants were randomized.</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 days</p>	<p>Results: Substance Abuse: Change in ASI (Drug Composite) at 12 weeks: Olanzapine vs Placebo - WMD = 0.03 (-0.03 , 0.09)</p> <p>Adverse Events: Olanzapine vs Placebo Medication Related Serious AE: 0.0%(0/15) vs 0.0%(0/15)</p> <p>Withdrawals: Olanzapine vs Placebo Withdrawals:13.3%(2/15) vs 6.7%(1/15)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Entering: 30 Withdrawn: NR Lost to follow-up: NR Analyzed: 27</p> <p>Method of AE assessment: Monitored</p>		
<p>Levin et al. 1999²⁶⁸</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: NR Eligible: 14 Entering: 14 Withdrawn: 4 Lost to follow-up: 0 Analyzed: 10</p>	<p>Inclusion criteria: Cocaine dependence</p> <p>Exclusion criteria: Alcohol, opiate or sedative dependence, MD on dysthymia, axis I disorder requiring treatment</p> <p>Interventions: Placebo for 6 weeks vs Risperidone 1-6 mg/days frequency not reported for 12 weeks</p> <p>Run-in/wash-out period: Run-in: Placebo for 2 week(s).</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 3, 7 days</p>	<p>Results: Substance Abuse: Change in Reduction in Use (Urine) at 6 weeks: Risperidone vs Placebo - WMD = 0.10 (-0.22 , 0.42)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Monitored		
<p>Lile et al. 2008²⁶¹</p> <p>Substance abuse</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: CCT only</p> <p>Setting: Single setting</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry</p> <p>Screened: 12 Eligible: 12 Entering: 24 Withdrawn: 6 Lost to follow-up: 0 Analyzed: 12</p> <p>Method of AE assessment: Monitored</p>	<p>Inclusion criteria: Cocaine dependence, no other psychiatric diagnosis</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 10 days vs Aripiprazole 15 mg/days fixed single dose for 10 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Adverse Events: Aripiprazole Extrapyramidal Symptoms During Maintenance: 8.3%(1/12)</p> <p>Withdrawals: Aripiprazole Withdrawals:50.0%(6/12) Withdrawals Due To Adverse Events:8.3%(1/12)</p>
<p>Newton et al. 2008²⁷²</p> <p>Substance abuse</p>	<p>Inclusion criteria: Methamphetamine dependent, not seeking treatment, aged 18-45, had normal physical examinations, EKG's and clinical lab</p>	<p>Results: Substance Abuse: Change in BDI at 2 weeks: Aripiprazole vs Placebo - WMD = 3.62 (-4.29 , 11.53)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 3</p> <p>Age: Mean: 30</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry, Hispanic</p> <p>Screened: NR Eligible: NR Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: 16</p> <p>Method of AE assessment: Monitored</p>	<p>assessments.</p> <p>Exclusion criteria: History of asthma, pregnancy, prior adverse reaction to methamphetamine or aripiprazole, history of seizure disorder, head trauma, dependent on other drugs (except nicotine), other axis I psychiatric disorder</p> <p>Interventions: Placebo for 14 days vs Aripiprazole 15 mg/days fixed single dose for 14 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 14 days</p>	<p>Adverse Events: Aripiprazole vs Placebo At Least One AE: 87.5%(7/8) vs 75.0%(6/8) Restlessness: 37.5%(3/8) vs 0.0%(0/8) Severe AE: 25.0%(2/8) vs 12.5%(1/8) Tremor: 50.0%(4/8) vs 25.0%(2/8)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:0.0%(0/8) vs 0.0%(0/8)</p>
<p>Reid et al. 2005²⁶⁵</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p>	<p>Inclusion criteria: Standardized MDD CREST study inclusion criteria</p> <p>Exclusion criteria: Clinically significant medical condition, standardized MDD CREST study exclusion criteria</p>	<p>Results: Substance Abuse: Change in ASI (Drug Composite) at 8 weeks: Olanzapine vs Placebo - WMD = 0.02 (-0.23 , 0.27)</p> <p>Adverse Events: Carnitine+CoQ10 vs Olanzapine vs Placebo vs Valproate Abdominal Pain: 12.5%(2/16) vs 5.6%(1/18) vs 6.3%(1/16) vs 27.8%(5/18) Anxiety: 0.0%(0/16) vs 0.0%(0/18) vs 0.0%(0/16) vs 11.1%(2/18) Arthralgia: 6.3%(1/16) vs 5.6%(1/18) vs 6.3%(1/16) vs 11.1%(2/18)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Multi-center, VA Healthcare System</p> <p>Jadad: 1</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Caucasian, African Ancestry, Hispanic, Other-NOS</p> <p>Screened: 135 Eligible: 68 Entering: NR Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>	<p>Interventions: Placebo 2 tablets/days fixed single dose for 8 weeks vs Olanzapine 5-10 mg/days fixed titration schedule for 8 weeks vs Valproate 800-1500 mg/days fixed titration schedule for 8 weeks vs Other, Carnitine + Carnitine + CoQ 10 200+500 mg/days fixed single dose for 8 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14, 21, 28, 35, 42, 49, 56 days</p>	<p>Asthenia: 12.5%(2/16) vs 5.6%(1/18) vs 12.5%(2/16) vs 11.1%(2/18) At Least One AE: 75.0%(12/16) vs 83.3%(15/18) vs 93.8%(15/16) vs 83.3%(15/18) Back Pain: 12.5%(2/16) vs 11.1%(2/18) vs 0.0%(0/16) vs 16.7%(3/18) Body Pain: 6.3%(1/16) vs 16.7%(3/18) vs 6.3%(1/16) vs 5.6%(1/18) Diarrhea: 6.3%(1/16) vs 5.6%(1/18) vs 25.0%(4/16) vs 33.3%(6/18) Dizziness: 6.3%(1/16) vs 16.7%(3/18) vs 31.3%(5/16) vs 5.6%(1/18) Dry Mouth: 18.8%(3/16) vs 0.0%(0/18) vs 0.0%(0/16) vs 11.1%(2/18) Dyspepsia: 0.0%(0/16) vs 5.6%(1/18) vs 18.8%(3/16) vs 11.1%(2/18) Ecchymosis: 12.5%(2/16) vs 0.0%(0/18) vs 12.5%(2/16) vs 0.0%(0/18) Fever: 0.0%(0/16) vs 0.0%(0/18) vs 12.5%(2/16) vs 11.1%(2/18) Flu Syndrome: 12.5%(2/16) vs 11.1%(2/18) vs 18.8%(3/16) vs 11.1%(2/18) Headache: 25.0%(4/16) vs 22.2%(4/18) vs 18.8%(3/16) vs 27.8%(5/18) Insomnia: 12.5%(2/16) vs 11.1%(2/18) vs 25.0%(4/16) vs 11.1%(2/18) Myalgia: 12.5%(2/16) vs 0.0%(0/18) vs 6.3%(1/16) vs 0.0%(0/18) Nausea: 12.5%(2/16) vs 0.0%(0/18) vs 31.3%(5/16) vs 5.6%(1/18) Somnolence: 18.8%(3/16) vs 44.4%(8/18) vs 25.0%(4/16) vs 38.9%(7/18) Thirst: 18.8%(3/16) vs 0.0%(0/18) vs 0.0%(0/16) vs 11.1%(2/18) Olanzapine vs Placebo vs Valproate Vomiting: 5.6%(1/18) vs 12.5%(2/16) vs 0.0%(0/18)</p>
<p>Smelson et al. 1997²⁶⁷</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p>	<p>Inclusion criteria: Recently cocaine-withdrawn patients, met DSM-IV criteria for cocaine dependence, admitted to a locked inpatient substance abuse treatment program</p> <p>Exclusion criteria: History of opiate, barbiturate, benzodiazepine, marijuana or alcohol dependence, met DSM-IV criteria for a concurrent Axis I disorder, currently taking medication that could affect the central nervous system, history of seizures, cognitive</p>	<p>Results: Substance Abuse: Change in Reduction in Use (Self Report) at 4 weeks: Risperidone vs Placebo - WMD = 4.40 (-2.68 , 11.48)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Design: CCT only</p> <p>Setting: Single setting</p> <p>Jadad: 0</p> <p>Age: Not reported</p> <p>Sex: 100% Male</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: NR</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Not reported</p>	<p>impairment, head trauma, Beck Depression Inventory>16</p> <p>Interventions: Control Group vs Risperidone 1-4 mg/days flexible dose for duration not reported</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7 days</p>	
<p>Smelson et al. 2004²⁷⁰</p> <p>Substance abuse</p> <p>Risperidone</p> <p>Location: US</p> <p>Trial:</p> <p>Funding source: Government, Industry</p> <p>Design: RCT only</p> <p>Setting: Single setting, VA Healthcare System</p> <p>Jadad: 3</p>	<p>Inclusion criteria: Met DSM-IV criteria for cocaine dependence, reported using at least 6g of cocaine in the past month, responded to cue-exposure with increased craving</p> <p>Exclusion criteria: Met DSM-IV criteria for an additional Axis I disorder, history of alcohol, opiate, barbiturate, benzodiazapine or marijuana dependence, taking medication that could affect central nervous system, history of seizures</p> <p>Interventions: Placebo for 2 weeks vs Risperidone 1-2 mg/days flexible dose for 2 weeks</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p> <p>Withdrawals: Placebo vs Risperidone Withdrawals:12.5%(2/16) vs 5.3%(1/19) Withdrawals Due To Adverse Events:0.0%(0/16) vs 5.3%(1/19)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Age: Mean: 41</p> <p>Sex:</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Entering: 35 Withdrawn: 3 Lost to follow-up: 0 Analyzed: 32</p> <p>Method of AE assessment: Reported spontaneously by patient</p>	<p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7, 14 days</p>	
<p>Stoops et al. 2007²⁶²</p> <p>Substance abuse</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: CCT only</p> <p>Setting: Single setting</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p>	<p>Inclusion criteria: Current crack cocaine users</p> <p>Exclusion criteria: Not for any other current psychiatric diagnosis</p> <p>Interventions: Placebo for 7 days vs Aripiprazole 10 mg/days fixed single dose for 7 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 7 days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Race: Caucasian, African Ancestry</p> <p>Screened: NR Eligible: 8 Entering: NR Withdrawn: 0 Lost to follow-up: 0 Analyzed: NR</p> <p>Method of AE assessment: Monitored</p>		
<p>Tiihonen et al.2007²⁷¹</p> <p>Substance abuse</p> <p>Aripiprazole</p> <p>Location: Western Europe</p> <p>Trial: Not reported</p> <p>Funding source: Government, Hospital</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 1</p> <p>Age: Mean: 36</p> <p>Sex: Mixed</p> <p>Race: Caucasian</p> <p>Screened: NR Eligible: NR Entering: 53</p>	<p>Inclusion criteria: Aged 18 - 65, amphetamine/methamphetamine dependence recent and accustomed intravenous amphetamine / methamphetamine use.</p> <p>Exclusion criteria: Not reported</p> <p>Interventions: Placebo for 20 weeks vs Aripiprazole 15 mg/days fixed single dose for 20 weeks vs Other, Methylphenidate 18-54 mg/days fixed titration schedule for 20 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 140 days</p>	<p>Results: Substance Abuse: Change in Proportion of amphetamine-positive urine screens at 20 weeks: Methylphenidate vs Placebo - RR = 2.25 (0.85 , 5.92)</p> <p>Substance Abuse: Change in Proportion of amphetamine-positive urine screens at 20 weeks: Aripiprazole vs Placebo - RR = 0.11 (0.01 , 1.92)</p> <p>Adverse Events: Placebo vs Aripiprazole vs Methylphenidate Transient Ischemic Attack (Attributed To Continued Amphetamine Use): 0.0%(0/17) vs 5.3%(1/19) vs 0.0%(0/17)</p> <p>Withdrawals: Aripiprazole Withdrawals:10.5%(2/19) Placebo vs Aripiprazole vs Methylphenidate Ransient Increase Of Liver Enzymes (Attributed To Recently Started HIV Medications) And Withdrawn:0.0%(0/17) vs 5.3%(1/19) vs 0.0%(0/17) Withdrawals Due To Adverse Events:0.0%(0/17) vs 10.5%(2/19) vs 0.0%(0/17)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Withdrawn: 2 Lost to follow-up: NR Analyzed: 17</p> <p>Method of AE assessment: Not reported</p>		
<p>Voronin et al. 2008²⁵³</p> <p>Substance abuse</p> <p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: University</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 4</p> <p>Age: Mean: 27</p> <p>Sex: 80-99% Male</p> <p>Race: Caucasian, African Ancestry, Native American</p> <p>Screened: NR Eligible: NR Entering: 30 Withdrawn: 0 Lost to follow-up: 0 Analyzed: 30</p>	<p>Inclusion criteria: Aged 21-65, alcohol dependence, non treatment seeking.</p> <p>Exclusion criteria: Current DSM-IV criteria for drug dependence except nicotine, other major DSM-IV Axis I disorders, psychoactive medication or substance abuse (except marijuana), past history of alcohol-related medical illness, liver enzymes \geq 2.5 times above normal, or significant health problems.</p> <p>Interventions: Placebo for 8 days vs Aripiprazole 5-15 mg/days fixed titration schedule for 8 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 6, 8 days</p>	<p>Results: Substance Abuse: Change in Complete Abstinence (Alcohol) at 0 weeks: Aripiprazole vs Placebo - RR = 1.67 (0.48 , 5.76)</p> <p>Adverse Events: Aripiprazole vs Placebo Constipation (Mild): 20.0%(3/15) vs 0.0%(0/15) Constipation (Moderate): 6.7%(1/15) vs 0.0%(0/15) Constipation (Severe): 0.0%(0/15) vs 0.0%(0/15) Day Time Sleepiness (Mild): 33.3%(5/15) vs 73.3%(11/15) Day Time Sleepiness (Moderate): 40.0%(6/15) vs 13.3%(2/15) Day Time Sleepiness (Severe): 26.7%(4/15) vs 0.0%(0/15) Feeling Depressed (Mild): 0.0%(0/15) vs 13.3%(2/15) Feeling Depressed (Moderate): 0.0%(0/15) vs 6.7%(1/15) Feeling Depressed (Severe): 0.0%(0/15) vs 0.0%(0/15) Nervousness (Mild): 40.0%(6/15) vs 0.0%(0/15) Nervousness (Moderate): 6.7%(1/15) vs 13.3%(2/15) Nervousness (Severe): 0.0%(0/15) vs 0.0%(0/15) Trouble Sleeping (Mild): 33.3%(5/15) vs 40.0%(6/15) Trouble Sleeping (Moderate): 46.7%(7/15) vs 0.0%(0/15) Trouble Sleeping (Severe): 6.7%(1/15) vs 6.7%(1/15)</p> <p>Withdrawals: Aripiprazole vs Placebo Withdrawals:0.0%(0/15) vs 0.0%(0/15) Withdrawals Due To Adverse Events:0.0%(0/15) vs 0.0%(0/15)</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
Method of AE assessment: Elicited by investigator		
<p>Hutchison et al. 2001²⁵⁸</p> <p>Substance abuse</p> <p>Olanzapine</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Government</p> <p>Design: RCT only</p> <p>Setting: Not reported</p> <p>Jadad: 3</p> <p>Age: Mean: 23</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: 26</p> <p>Entering: 26</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Not reported</p>	<p>Inclusion criteria: Reported drinking ≥ 2 times/week, ≥ 3 drinks / occasion (2 for women), age ≥ 21 years old</p> <p>Exclusion criteria: Reported ever having received treatment for alcohol problems, have history of cardiac illness, reported hearing loss, were taking medications contraindicated for concurrent use with olanzapine, breath alcohol level >0</p> <p>Interventions: Placebo for 2 days vs Olanzapine 5 mg/days fixed single dose for 2 days</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 1, 7 days</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p>
<p>Anton et al. 2006²⁵⁴</p> <p>Substance abuse</p>	<p>Inclusion criteria: Medically stable, alcohol dependent, outpatients</p>	<p>Results: Substance Abuse: Insufficient data to calculate an effect size</p>

Citation and Study Information	Eligibility, Interventions, Outcomes	Results, Adverse Events, and Withdrawals
<p>Aripiprazole</p> <p>Location: US</p> <p>Trial: Not reported</p> <p>Funding source: Not reported</p> <p>Design: RCT only</p> <p>Setting: Multi-center</p> <p>Jadad: 2</p> <p>Age: Not reported</p> <p>Sex: Mixed</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Entering: NR</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: NR</p> <p>Method of AE assessment: Not reported</p>	<p>Exclusion criteria: Other substance abuse</p> <p>Interventions: Placebo for 12 weeks vs Aripiprazole <=30 mg/days frequency not reported for 12 weeks</p> <p>Run-in/wash-out period: Not reported</p> <p>Comorbidities: None</p> <p>Timing of outcome assessment: 84 days</p>	

AE=Adverse Event, NR=Not Reported

Quality

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Armenteros et al. 2007 ⁷⁷ ADHD Risperidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Tramontina et al. 2009 ⁷⁹ ADHD Aripiprazole	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Yes</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Bandelow et al. 2009 ⁸⁸ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Barnett et al. 2002 ⁸³ Anxiety Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Don't know Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Brawman-Mintzer et al. 2005 ⁹⁸ Anxiety Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Donahue et al. 2009 ⁹⁵ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Hirschfeld et al. 2006 ⁹² Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Pandina et al. 2007 ⁹⁹ Anxiety Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Yes	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Pollack et al. 2006 ⁸⁴ Anxiety Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Simon et al. 2008 ⁸⁵ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Vaishnavi et al. 2007 ⁸⁹ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Merideth et al. 2008 ⁸⁷ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Joyce et al. 2008 ⁹⁴ Anxiety Quetiapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Don't know</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Lohoff et al. 2010 ¹⁰⁰ Anxiety Ziprasidone	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Katzman et al. 2011 ⁹³ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? No	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? No
Altamura et al. 2011 ⁹⁰ Anxiety Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Don't know Was the care provider masked? Don't know Were patients masked? Don't know	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Mintzer et al. 2007 ¹⁰⁷ Dementia/Agitation Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Naber et al. 2007 ¹²⁸ Dementia/Agitation Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Zhong et al. 2007 ¹²² Dementia/Agitation Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Yes	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Streim et al. 2008 ¹⁰⁸ Dementia/Agitation Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Rappaport et al. 2009 ¹⁰⁹ Dementia/Agitation Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Paleacu et al. 2008 ¹²³ Dementia/Agitation Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Mintzer et al. 2006 ¹²⁹ Dementia/Agitation Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? No Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Cutler et al. 2009 ¹⁷¹ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Weisler et al. 2009 ¹⁷² Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Chaput et al. 2008 ¹⁵⁸ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Don't know Was the care provider masked? Don't know Were patients masked? Don't know	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
AstraZeneca 2008 ¹⁷³ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
AstraZeneca 2008 ¹⁶⁹ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
AstraZeneca 2007 ¹⁶⁸ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Bortnick et al. 2011 ¹⁷⁰ Depression Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Bissada et al. 2008 ¹⁸⁰ Eating disorder Olanzapine	Was the study described as randomized? No Was the method of randomization adequate? Yes Was the treatment allocation concealed? Yes	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Brambilla et al. 2007 ¹⁸² Eating disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Brambilla et al. 2007 ¹⁸³ Eating disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Gaskill et al. 2001 ¹⁸⁴ Eating disorder Olanzapine	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? No	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Don't know

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Court et al. 2010 ¹⁸⁵ Eating disorder Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Tassniyom et al. 2010 ³⁰⁷ Insomnia Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Padala et al. 2006 ²³³ PTSD Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Rothbaum et al. 2008 ²³⁷ PTSD Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Hamner et al. 2009 ²³⁹ PTSD Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Nickel et al. 2007 ²¹⁹ Personality disorder Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Open If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? No Was the care provider masked? No Were patients masked? No	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Pascual et al. 2008 ²²² Personality disorder Ziprasidone	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
McClure et al. 2009 ²²⁷ Personality disorder Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Schulz et al. 2008 ²²³ Personality disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Linehan et al. 2008 ²²⁴ Personality disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
van den Broek et al. 2008 ²²¹ Personality disorder Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Don't know Was the care provider masked? Don't know Were patients masked? Don't know	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? No Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Zanarini et al. 2007 ²²⁰ Personality disorder Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Kampman et al. 2007 ²⁵⁹ Substance abuse Quetiapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Loebel et al. 2008 ²⁶⁹ Substance abuse Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
<p>Anton et al. 2008²⁵²</p> <p>Substance abuse</p> <p>Aripiprazole</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
<p>Grabowski et al. 2000²⁶⁶</p> <p>Substance abuse</p> <p>Risperidone</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Grabowski et al. 2004 ²⁷⁴ Substance abuse Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Guardia et al. 2004 ²⁵⁶ Substance abuse Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Yes	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? No Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Hamilton et al. 2009 ²⁶³ Substance abuse Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Yes</p> <p>Was the treatment allocation concealed? Yes</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? Don't know</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? No</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Hutchison et al. 2006 ²⁵⁷ Substance abuse Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Single blind, patient</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Kampman et al. 2003 ²⁶⁴ Substance abuse Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Yes Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes
Levin et al. 1999 ²⁶⁸ Substance abuse Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Lile et al. 2008 ²⁶¹ Substance abuse Aripiprazole	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Newton et al. 2008 ²⁷² Substance abuse Aripiprazole	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Yes Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Don't know Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Reid et al. 2005 ²⁶⁵ Substance abuse Olanzapine	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? Yes	How is blinding described? Not described If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? No Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Yes Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Smelson et al. 1997 ²⁶⁷ Substance abuse Risperidone	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Don't know	How is blinding described? Single blind, outcome assessment If reported, was the method of double-blinding appropriate? Not applicable Was the outcome assessor masked? Yes Was the care provider masked? Don't know Were patients masked? No	Was the dropout rate described and the reason given? No Was the dropout rate acceptable? Don't know Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Smelson et al. 2004 ²⁷⁰ Substance abuse Risperidone	Was the study described as randomized? Yes Was the method of randomization adequate? Don't know Was the treatment allocation concealed? Don't know	Were groups similar at baseline? No	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Don't know Was the outcome assessment timing similar in all groups? Yes
Stoops et al. 2007 ²⁶² Substance abuse Aripiprazole	Was the study described as randomized? No Was the method of randomization adequate? No Was the treatment allocation concealed? No	Were groups similar at baseline? Don't know	How is blinding described? Double blind If reported, was the method of double-blinding appropriate? Not described Was the outcome assessor masked? Yes Was the care provider masked? Yes Were patients masked? Yes	Was the dropout rate described and the reason given? Yes Was the dropout rate acceptable? Yes Were all randomized participants analyzed? Yes	Were cointerventions avoided or similar? Don't know Was the compliance acceptable in all groups? Yes Was the outcome assessment timing similar in all groups? Yes

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
<p>Tiihonen et al. 2007²⁷¹</p> <p>Substance abuse</p> <p>Aripiprazole</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? No</p>	<p>How is blinding described? Not described</p> <p>If reported, was the method of double-blinding appropriate? Not applicable</p> <p>Was the outcome assessor masked? Don't know</p> <p>Was the care provider masked? Don't know</p> <p>Were patients masked? Don't know</p>	<p>Was the dropout rate described and the reason given? Don't know</p> <p>Was the dropout rate acceptable? Don't know</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
<p>Voronin et al. 2008²⁵³</p> <p>Substance abuse</p> <p>Aripiprazole</p>	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Yes</p> <p>Was the dropout rate acceptable? Yes</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

Study	Treatment allocation	Groups similar at baseline?	Blinding	Dropouts	Other sources of potential bias
Hutchison et al. 2001 ²⁵⁸ Substance abuse Olanzapine	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Yes</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Yes</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? Don't know</p> <p>Was the dropout rate acceptable? Don't know</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Yes</p> <p>Was the compliance acceptable in all groups? Yes</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>
Anton et al. 2006 ²⁵⁴ Substance abuse Aripiprazole	<p>Was the study described as randomized? Yes</p> <p>Was the method of randomization adequate? Don't know</p> <p>Was the treatment allocation concealed? Don't know</p>	<p>Were groups similar at baseline? Don't know</p>	<p>How is blinding described? Double blind</p> <p>If reported, was the method of double-blinding appropriate? Not described</p> <p>Was the outcome assessor masked? Yes</p> <p>Was the care provider masked? Yes</p> <p>Were patients masked? Yes</p>	<p>Was the dropout rate described and the reason given? No</p> <p>Was the dropout rate acceptable? No</p> <p>Were all randomized participants analyzed? Yes</p>	<p>Were cointerventions avoided or similar? Don't know</p> <p>Was the compliance acceptable in all groups? Don't know</p> <p>Was the outcome assessment timing similar in all groups? Yes</p>

AE=Adverse Event, NR=Not Reported

Appendix E. Excluded Studies

Reject Descriptive

- U.S. Food and Drug Administration. Postmarket Drug Safety Information for Patients and Providers. FDA Public Health Advisory. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Cited December 12, 2009.
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Appendix F. Adverse Events Analyses

Table F1. Children and adolescents—placebo controlled trials

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH	95% CI NNH
			# adverse events	sample size	# adverse events	sample size				
Appetite or Weight/Decrease	Aripiprazole	1	15	25	13	18	1.71	(0.40, 8.15)	NC	NC
Appetite or Weight/Decrease	Risperidone	1	1	18	1	16	1.13	(0.01, 94.13)	NC	NC
Appetite or Weight/Increase	Aripiprazole	1	22	25	14	18	0.49	(0.06, 3.35)	NC	NC
Appetite or Weight/Increase	Risperidone	2	0	31	8	28	+Inf	(2.52, Inf+)	4.00	(2.00, 8.00)
Cardiovascular	Aripiprazole	1	10	25	9	18	1.49	(0.37, 6.03)	NC	NC
Constitutional/Fever or Infection	Aripiprazole	1	5	25	5	18	1.52	(0.29, 8.12)	NC	NC
Dermatologic	Aripiprazole	1	14	25	11	18	1.23	(0.31, 5.11)	NC	NC
Endocrine	Ziprasidone	1	0	12	1	16	+Inf	(0.02, Inf+)	NC	NC
Endocrine/Prolactin	Ziprasidone	1	0	12	5	16	+Inf	(0.78, Inf+)	NC	NC
Gastrointestinal	Aripiprazole	1	25	25	18	18	NC	NC	NC	NC
Gastrointestinal	Risperidone	2	5	31	6	28	1.45	(0.28, 7.82)	NC	NC
HEENT	Aripiprazole	1	25	25	18	18	NC	NC	NC	NC
HEENT/Eye	Aripiprazole	1	14	25	12	18	1.56	(0.38, 6.81)	NC	NC
HEENT/Eye	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)	NC	NC
Musculoskeletal	Aripiprazole	1	6	25	3	18	0.64	(0.09, 3.62)	NC	NC
Neuro	Aripiprazole	1	25	25	18	18	NC	NC	NC	NC
Neuro	Risperidone	1	3	18	0	16	0.00	(0.00, 2.64)	NC	NC
Neuro/Fatigue	Aripiprazole	1	14	25	15	18	3.81	(0.78, 25.71)	NC	NC
Neuro/Fatigue	Risperidone	1	1	18	6	16	9.54	(0.95, 496.02)	NC	NC
Neuro/Movement Disorder/Akathisia	Aripiprazole	1	3	25	2	18	0.92	(0.07, 9.02)	NC	NC
Neuro/Movement Disorder/Akathisia	Ziprasidone	1	0	12	1	16	+Inf	(0.02, Inf+)	NC	NC
Neuro/Movement Disorder/EPS	Aripiprazole	1	8	25	15	18	9.96	(2.03, 69.36)	2.00	(1.00, 4.00)
Neuro/Sedation	Aripiprazole	1	25	25	18	18	NC	NC	NC	NC
Neuro/Sedation	Risperidone	2	3	31	4	28	1.53	(0.24, 11.33)	NC	NC
Neuro/Sedation	Ziprasidone	1	5	12	12	16	3.97	(0.66, 28.56)	NC	NC
Neuro/Sensory	Aripiprazole	1	13	25	8	18	0.74	(0.18, 2.93)	NC	NC

Table F1. Children and adolescents—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH	95% CI NNH
			# adverse events	sample size	# adverse events	sample size				
Psychiatric	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)	NC	NC
Psychiatric/Aggression	Aripiprazole	1	9	25	10	18	2.18	(0.55, 9.15)	NC	NC
Psychiatric/Agitation	Risperidone	1	0	13	1	12	+Inf	(0.03, Inf+)	NC	NC
Psychiatric/Anxiety	Aripiprazole	1	25	25	18	18	NC	NC	NC	NC
Psychiatric/Cognitive	Aripiprazole	1	10	25	6	18	0.76	(0.17, 3.13)	NC	NC
Psychiatric/Cognitive	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)	NC	NC
Psychiatric/Depression	Aripiprazole	1	14	25	8	18	0.64	(0.16, 2.50)	NC	NC
Psychiatric/Mania	Aripiprazole	1	8	25	5	18	0.82	(0.17, 3.68)	NC	NC
Psychiatric/Sexual/Decreased Function	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)	NC	NC
Psychiatric/Sleep	Risperidone	1	1	18	1	16	1.13	(0.01, 94.13)	NC	NC
Psychiatric/Suicidal Ideation	Aripiprazole	1	5	25	5	18	1.52	(0.29, 8.12)	NC	NC
Pulmonary	Aripiprazole	1	9	25	7	18	1.13	(0.27, 4.68)	NC	NC
Sweating	Aripiprazole	1	11	25	10	18	1.57	(0.40, 6.41)	NC	NC
Urinary	Aripiprazole	1	2	25	1	18	0.68	(0.01, 14.13)	NC	NC

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Table F2. Children and adolescents—atypical versus clonidine

Adverse Events	Drug	# of studies	Clonidine		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
HEENT/Decreased Salivation	Risperidone	1	1	12	0	9	0.00	(0.00, 52.00)
Neuro	Risperidone	1	2	12	1	9	0.64	(0.01, 14.44)
Neuro/Movement Disorder/EPS	Risperidone	1	1	12	2	9	2.97	(0.13, 201.94)
Neuro/Sedation	Risperidone	1	5	12	1	9	0.19	(0.00, 2.32)

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; OR = odds ratio

Table F3. Children and adolescents—atypical versus conventionals

Adverse Events	Drug	# of studies	Conventional		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Increase	Risperidone	1	20	24	22	26	1.10	(0.18, 6.75)
Neuro/Fatigue	Risperidone	1	9	24	10	26	1.04	(0.29, 3.81)
Neuro/Headache	Risperidone	1	2	24	5	26	2.57	(0.37, 29.80)
Neuro/Movement Disorder	Risperidone	1	5	24	2	26	0.32	(0.03, 2.25)
Neuro/Movement Disorder/EPS	Risperidone	1	8	24	4	26	0.37	(0.07, 1.68)
Neuro/Sedation	Risperidone	1	10	24	12	26	1.20	(0.34, 4.25)
Psychiatric/Depression	Risperidone	1	6	24	8	26	1.33	(0.33, 5.68)
Psychiatric/Sleep	Risperidone	1	7	24	1	26	0.10	(0.00, 0.90)
Trauma	Risperidone	1	6	24	1	26	0.12	(0.00, 1.16)

CI = confidence interval; EPS = extrapyramidal symptoms; OR = odds ratio

Table F4. Non-elderly adults—placebo controlled trials

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Accidental Overdose	Aripiprazole	1	1	146	0	149	0.00	(0.00, 38.21)	NC
Alcohol Related	Olanzapine	1	0	159	1	155	+Inf	(0.03, Inf+)	NC
Appetite or Weight/Decrease	Olanzapine	1	1	159	0	155	0.00	(0.00, 40.00)	NC
Appetite or Weight/Decrease	Quetiapine	4	7	634	16	925	1.56	(0.59, 4.56)	NC
Appetite or Weight/Decrease	Ziprasidone	1	1	21	1	41	0.51	(0.01, 41.19)	NC
Appetite or Weight/Increase	Aripiprazole	4	8	686	35	701	4.18	(1.88, 10.56)	35
Appetite or Weight/Increase	Olanzapine	11	103	819	382	818	11.30	(8.22, 15.74)	3
Appetite or Weight/Increase	Quetiapine	13	90	1846	279	2887	2.71	(2.07, 3.58)	16
Appetite or Weight/Increase	Risperidone	4	5	197	24	237	3.78	(1.35, 13.09)	21
Appetite or Weight/Increase	Ziprasidone	2	2	113	5	251	1.24	(0.19, 13.59)	NC
Cardiovascular	Olanzapine	2	8	125	11	124	1.63	(0.51, 5.57)	NC
Cardiovascular	Quetiapine	2	4	192	1	186	0.26	(0.01, 2.60)	NC
Cardiovascular	Risperidone	1	1	133	4	141	3.84	(0.37, 191.22)	NC
Cardiovascular	Ziprasidone	1	0	48	2	91	+Inf	(0.10, Inf+)	NC
Cardiovascular/BP/Decrease	Olanzapine	3	22	433	20	422	1.02	(0.44, 2.38)	NC
Cardiovascular/BP/Decrease	Quetiapine	5	31	950	58	950	2.01	(1.25, 3.30)	27
Cardiovascular/BP/Decrease	Ziprasidone	1	0	92	3	210	+Inf	(0.18, Inf+)	NC
Cardiovascular/BP/Increase	Olanzapine	1	6	377	2	370	0.34	(0.03, 1.90)	NC
Cardiovascular/BP/Increase	Quetiapine	3	81	568	122	568	1.71	(1.22, 2.39)	13
Cardiovascular/BP/Increase	Risperidone	1	3	133	0	141	0.00	(0.00, 2.27)	NC
Cardiovascular/Rhythm	Aripiprazole	1	1	146	0	149	0.00	(0.00, 38.21)	NC
Cardiovascular/Rhythm	Olanzapine	1	1	377	1	370	1.02	(0.01, 80.20)	NC
Cardiovascular/Rhythm	Quetiapine	4	45	727	60	885	1.32	(0.86, 2.03)	NC
Cardiovascular/Rhythm	Risperidone	1	0	11	1	14	+Inf	(0.02, Inf+)	NC
Cardiovascular/Rhythm	Ziprasidone	1	0	21	1	41	+Inf	(0.01, Inf+)	NC
Constitutional/Fever or Infection	Aripiprazole	3	1	514	4	524	3.92	(0.39, 193.38)	NC
Constitutional/Fever or Infection	Olanzapine	1	5	16	2	18	0.29	(0.02, 2.14)	NC
Constitutional/Fever or Infection	Quetiapine	4	15	354	21	504	1.28	(0.61, 2.75)	NC
Death	Quetiapine	2	1	542	1	695	0.71	(0.01, 58.88)	NC
Dermatologic	Olanzapine	3	3	72	3	70	1.02	(0.13, 7.90)	NC
Dermatologic	Quetiapine	2	1	189	8	186	+Inf	(1.51, Inf+)	46
Dermatologic	Risperidone	1	0	9	1	11	+Inf	(0.02, Inf+)	NC
Dermatologic	Ziprasidone	2	2	69	7	132	1.87	(0.34, 18.94)	NC

Table F4. Non-elderly adults—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Endocrine	Olanzapine	2	15	190	31	184	2.37	(1.18, 4.94)	12
Endocrine	Quetiapine	1	1	148	5	298	2.50	(0.28, 119.45)	NC
Endocrine	Risperidone	1	0	12	1	19	+Inf	(0.02, Inf+)	NC
Endocrine	Ziprasidone	1	0	30	2	30	+Inf	(0.19, Inf+)	NC
Endocrine/Diabetes	Olanzapine	1	1	377	5	370	5.14	(0.57, 244.28)	NC
Endocrine/Diabetes	Quetiapine	6	11	1073	32	1753	1.47	(0.71, 3.28)	NC
Endocrine/Prolactin	Risperidone	1	0	10	1	15	+Inf	(0.02, Inf+)	NC
Gastrointestinal	Aripiprazole	6	86	727	90	742	1.03	(0.74, 1.43)	NC
Gastrointestinal	Olanzapine	11	126	863	99	859	0.72	(0.53, 0.98)	NC
Gastrointestinal	Quetiapine	18	499	2291	785	3514	1.08	(0.94, 1.24)	NC
Gastrointestinal	Risperidone	5	44	253	34	290	0.62	(0.36, 1.06)	NC
Gastrointestinal	Ziprasidone	5	71	212	149	392	1.00	(0.68, 1.48)	NC
HEENT	Olanzapine	1	1	31	2	29	2.20	(0.11, 136.07)	NC
HEENT	Quetiapine	9	102	1634	112	2171	0.90	(0.67, 1.20)	NC
HEENT	Risperidone	1	8	133	5	141	0.58	(0.14, 2.06)	NC
HEENT	Ziprasidone	1	1	48	4	91	2.15	(0.21, 108.65)	NC
HEENT/Decreased Salivation	Aripiprazole	1	11	178	6	184	0.51	(0.15, 1.55)	NC
HEENT/Decreased Salivation	Olanzapine	8	59	826	126	810	2.64	(1.86, 3.81)	12
HEENT/Decreased Salivation	Quetiapine	17	141	2084	961	3325	5.42	(4.46, 6.61)	7
HEENT/Decreased Salivation	Risperidone	5	9	241	30	281	2.99	(1.31, 7.54)	17
HEENT/Decreased Salivation	Ziprasidone	3	6	134	34	271	3.34	(1.31, 10.20)	15
HEENT/Eye	Aripiprazole	2	6	350	25	361	4.25	(1.68, 12.83)	25
HEENT/Eye	Olanzapine	1	5	100	1	101	0.19	(0.00, 1.77)	NC
HEENT/Eye	Quetiapine	4	9	467	29	769	2.09	(0.94, 5.11)	NC
HEENT/Eye	Risperidone	1	0	20	3	20	+Inf	(0.43, Inf+)	NC
HEENT/Eye	Ziprasidone	2	0	42	6	61	+Inf	(1.07, Inf+)	NC
Heme	Quetiapine	3	1	536	5	680	3.74	(0.40, 180.66)	NC
Increased Cholesterol	Quetiapine	3	73	528	149	1067	1.02	(0.74, 1.40)	NC
Infections	Aripiprazole	2	20	350	28	361	1.39	(0.74, 2.65)	NC
Infections	Quetiapine	4	42	722	46	1022	0.85	(0.53, 1.38)	NC
Infections	Risperidone	1	3	133	0	141	0.00	(0.00, 2.27)	NC
Infections	Ziprasidone	1	0	21	1	20	+Inf	(0.03, Inf+)	NC
Liver Function Test Abnormality	Aripiprazole	1	2	146	10	168	4.61	(0.93, 44.57)	NC
Liver Function Test Abnormality	Olanzapine	1	0	69	12	70	+Inf	(3.16, Inf+)	NC
Liver Function Test Abnormality	Quetiapine	1	2	216	0	216	0.00	(0.00, 5.32)	NC

Table F4. Non-elderly adults—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Liver Function Test Abnormality	Risperidone	1	0	11	1	14	+Inf	(0.02, Inf+)	NC
Liver Function Test Abnormality	Ziprasidone	1	0	48	1	91	+Inf	(0.01, Inf+)	NC
Metabolic Lab Abnormality	Quetiapine	3	32	537	108	903	2.20	(1.43, 3.47)	18
Musculoskeletal	Aripiprazole	1	1	178	0	184	0.00	(0.00, 37.73)	NC
Musculoskeletal	Olanzapine	3	14	59	14	59	1.01	(0.18, 5.62)	NC
Musculoskeletal	Quetiapine	5	29	748	60	906	1.86	(1.16, 3.06)	34
Musculoskeletal	Risperidone	2	8	190	6	195	0.62	(0.15, 2.21)	NC
Neuro	Aripiprazole	6	127	795	111	805	0.83	(0.62, 1.12)	NC
Neuro	Olanzapine	8	56	377	74	369	1.55	(1.00, 2.42)	17
Neuro	Quetiapine	19	508	2305	881	3551	1.24	(1.09, 1.43)	22
Neuro	Risperidone	6	63	261	54	301	0.72	(0.45, 1.15)	NC
Neuro	Ziprasidone	5	18	212	58	404	1.95	(1.06, 3.72)	16
Neuro/Fatigue	Aripiprazole	4	31	686	82	701	2.86	(1.83, 4.55)	15
Neuro/Fatigue	Olanzapine	7	43	737	80	720	2.06	(1.37, 3.12)	19
Neuro/Fatigue	Quetiapine	13	74	2010	289	3072	2.94	(2.20, 3.97)	18
Neuro/Fatigue	Risperidone	4	9	233	9	274	0.83	(0.28, 2.41)	NC
Neuro/Fatigue	Ziprasidone	2	0	69	8	111	+Inf	(1.59, Inf+)	NC
Neuro/Headache	Aripiprazole	1	0	146	1	149	+Inf	(0.03, Inf+)	NC
Neuro/Headache	Olanzapine	3	94	506	68	495	0.69	(0.48, 0.98)	NC
Neuro/Headache	Ziprasidone	2	40	140	68	301	0.72	(0.44, 1.17)	NC
Neuro/Movement Disorder	Olanzapine	2	8	56	8	52	1.33	(0.35, 5.13)	NC
Neuro/Movement Disorder	Quetiapine	2	23	320	42	464	1.99	(1.10, 3.66)	16
Neuro/Movement Disorder	Ziprasidone	1	0	30	0	30	NC	NC	NC
Neuro/Movement Disorder/Akathisia	Aripiprazole	5	24	769	190	779	11.78	(7.40, 19.61)	7
Neuro/Movement Disorder/Akathisia	Olanzapine	1	7	25	9	23	2.04	(0.50, 8.92)	NC
Neuro/Movement Disorder/Akathisia	Quetiapine	4	5	488	10	632	1.31	(0.38, 5.07)	NC
Neuro/Movement Disorder/Akathisia	Risperidone	1	0	18	1	19	+Inf	(0.02, Inf+)	NC
Neuro/Movement Disorder/Akathisia	Ziprasidone	3	9	161	36	321	2.11	(0.96, 5.15)	NC
Neuro/Movement Disorder/EPS	Aripiprazole	5	43	605	99	610	2.75	(1.83, 4.19)	11
Neuro/Movement Disorder/EPS	Olanzapine	3	18	65	17	71	0.87	(0.25, 2.97)	NC
Neuro/Movement Disorder/EPS	Quetiapine	7	35	1100	87	1466	2.62	(1.72, 4.06)	36

Table F4. Non-elderly adults—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Neuro/Movement Disorder/EPS	Risperidone	1	1	10	0	15	0.00	(0.00, 26.00)	NC
Neuro/Movement Disorder/EPS	Ziprasidone	3	6	161	28	321	3.12	(1.15, 10.62)	24
Neuro/Pain	Olanzapine	2	5	85	13	88	2.74	(0.86, 10.40)	NC
Neuro/Pain	Quetiapine	7	65	1107	128	1609	1.59	(1.13, 2.25)	35
Neuro/Pain	Risperidone	1	3	133	0	141	0.00	(0.00, 2.27)	NC
Neuro/Pain	Ziprasidone	2	12	140	26	301	1.02	(0.48, 2.29)	NC
Neuro/Sedation	Aripiprazole	7	73	810	160	820	3.03	(2.15, 4.32)	8
Neuro/Sedation	Olanzapine	14	127	904	279	901	2.95	(2.29, 3.82)	6
Neuro/Sedation	Quetiapine	18	373	2285	1668	3531	5.54	(4.78, 6.43)	3
Neuro/Sedation	Risperidone	8	25	290	54	336	2.43	(1.39, 4.34)	11
Neuro/Sedation	Ziprasidone	5	21	212	95	392	3.90	(2.15, 7.44)	6
Neuro/Sensory	Quetiapine	1	2	157	4	157	2.02	(0.29, 22.66)	NC
Neuro/Speech Disorder	Quetiapine	1	0	21	1	21	+Inf	(0.03, Inf+)	NC
Psychiatric	Aripiprazole	1	1	146	0	149	0.00	(0.00, 38.21)	NC
Psychiatric	Olanzapine	4	27	313	16	303	0.58	(0.27, 1.22)	NC
Psychiatric	Quetiapine	1	1	21	1	21	1.00	(0.01, 82.37)	NC
Psychiatric	Ziprasidone	1	5	21	24	41	4.41	(1.24, 18.48)	3
Psychiatric/Aggression	Olanzapine	3	16	288	8	280	0.49	(0.17, 1.25)	NC
Psychiatric/Agitation	Aripiprazole	7	28	803	108	813	4.26	(2.75, 6.80)	13
Psychiatric/Agitation	Olanzapine	3	31	288	19	280	0.57	(0.28, 1.11)	NC
Psychiatric/Agitation	Quetiapine	3	3	521	13	671	3.35	(0.90, 18.65)	NC
Psychiatric/Agitation	Ziprasidone	3	16	161	27	321	0.84	(0.42, 1.74)	NC
Psychiatric/Anxiety	Aripiprazole	4	28	270	57	268	2.40	(1.42, 4.12)	9
Psychiatric/Anxiety	Olanzapine	6	89	708	70	691	0.76	(0.53, 1.09)	NC
Psychiatric/Anxiety	Quetiapine	5	19	936	32	1314	1.36	(0.73, 2.58)	NC
Psychiatric/Apathy	Quetiapine	1	2	20	3	20	1.57	(0.16, 20.98)	NC
Psychiatric/Cognitive	Aripiprazole	1	3	146	14	149	4.92	(1.33, 27.29)	19
Psychiatric/Cognitive	Olanzapine	1	1	25	5	23	6.51	(0.64, 333.53)	NC
Psychiatric/Cognitive	Quetiapine	4	9	226	18	378	1.56	(0.64, 4.11)	NC
Psychiatric/Cognitive	Risperidone	1	0	133	3	141	+Inf	(0.39, Inf+)	NC
Psychiatric/Cognitive	Ziprasidone	1	0	21	2	20	+Inf	(0.20, Inf+)	NC
Psychiatric/Depression	Aripiprazole	2	15	98	9	93	0.57	(0.20, 1.54)	NC
Psychiatric/Depression	Olanzapine	3	12	259	11	254	0.91	(0.35, 2.38)	NC
Psychiatric/Depression	Quetiapine	2	8	180	16	327	1.78	(0.63, 5.52)	NC
Psychiatric/Depression	Ziprasidone	1	0	21	4	41	+Inf	(0.34, Inf+)	NC

Table F4. Non-elderly adults—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Psychiatric/Irritability	Quetiapine	7	50	1081	70	1739	0.82	(0.55, 1.23)	NC
Psychiatric/Irritability	Risperidone	1	0	57	1	54	+Inf	(0.03, Inf+)	NC
Psychiatric/Mania	Aripiprazole	1	11	83	5	78	0.40	(0.09, 1.45)	NC
Psychiatric/Mania	Quetiapine	1	7	181	9	361	0.63	(0.21, 2.04)	NC
Psychiatric/Self-Injurious Behavior	Aripiprazole	2	8	172	2	175	0.20	(0.02, 1.16)	NC
Psychiatric/Self-Injurious Behavior	Olanzapine	1	0	159	1	155	+Inf	(0.03, Inf+)	NC
Psychiatric/Serious	Ziprasidone	1	3	30	4	30	1.38	(0.21, 10.33)	NC
Psychiatric/Sexual/Decreased Function	Olanzapine	3	12	55	13	53	1.32	(0.48, 3.68)	NC
Psychiatric/Sexual/Decreased Function	Quetiapine	5	23	579	28	951	0.97	(0.48, 1.98)	NC
Psychiatric/Sexual/Decreased Function	Risperidone	3	4	28	1	37	0.19	(0.00, 2.07)	NC
Psychiatric/Sexual/Decreased Function	Ziprasidone	1	0	92	2	210	+Inf	(0.08, Inf+)	NC
Psychiatric/Sleep	Aripiprazole	2	24	98	25	93	1.21	(0.56, 2.66)	NC
Psychiatric/Sleep	Olanzapine	2	77	477	39	471	0.46	(0.30, 0.71)	NC
Psychiatric/Sleep	Quetiapine	6	46	607	34	906	0.57	(0.35, 0.93)	NC
Psychiatric/Sleep	Ziprasidone	3	15	161	28	342	0.82	(0.40, 1.72)	NC
Psychiatric/Suicidal Ideation	Aripiprazole	2	2	350	1	361	0.48	(0.01, 9.32)	NC
Psychiatric/Suicidal Ideation	Olanzapine	1	4	159	10	155	2.66	(0.75, 11.90)	NC
Psychiatric/Suicidal Ideation	Quetiapine	3	2	544	6	536	3.08	(0.55, 31.38)	NC
Psychiatric/Suicidal Ideation	Risperidone	2	0	22	2	34	+Inf	(0.12, Inf+)	NC
Pulmonary	Quetiapine	1	4	157	5	157	1.26	(0.27, 6.46)	NC
Pulmonary	Ziprasidone	1	2	48	8	91	2.21	(0.42, 22.18)	NC
Sweating	Quetiapine	6	31	524	28	828	0.75	(0.41, 1.37)	NC
Thirst	Olanzapine	1	0	5	1	7	+Inf	(0.02, Inf+)	NC
Thirst	Quetiapine	3	0	310	6	465	+Inf	(0.97, Inf+)	NC
Trauma	Aripiprazole	1	1	178	0	184	0.00	(0.00, 37.73)	NC
Trauma	Quetiapine	1	1	148	4	298	2.00	(0.20, 99.16)	NC
Urinary	Quetiapine	3	7	571	20	724	2.31	(0.92, 6.59)	NC
Urinary	Risperidone	1	0	8	1	8	+Inf	(0.03, Inf+)	NC

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Table F5. Non-elderly adults—atypicals versus conventionals

Adverse Events	Drug	# of studies	Conventional		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Olanzapine	1	115	636	149	1306	0.58	(0.44, 0.77)
Appetite or Weight/Increase	Aripiprazole	1	14	431	44	859	1.61	(0.85, 3.21)
Appetite or Weight/Increase	Olanzapine	4	112	808	404	1486	2.72	(2.13, 3.50)
Cardiovascular/BP/Decrease	Olanzapine	1	1	7	0	8	0.00	(0.00, 34.12)
Cardiovascular/Rhythm	Olanzapine	1	63	636	86	1306	0.64	(0.45, 0.92)
Constitutional	Olanzapine	1	36	636	45	1306	0.59	(0.37, 0.96)
Constitutional/Fever or Infection	Olanzapine	1	48	636	56	1306	0.55	(0.36, 0.84)
Endocrine/Diabetes	Olanzapine	1	0	26	0	35	NC	NC
Gastrointestinal	Olanzapine	2	161	768	209	1437	0.60	(0.48, 0.77)
HEENT/Decreased Salivation	Olanzapine	1	103	636	290	1306	1.48	(1.15, 1.91)
HEENT/Eye	Olanzapine	1	96	636	139	1306	0.67	(0.50, 0.90)
HEENT/Increased Salivation	Olanzapine	1	124	636	113	1306	0.39	(0.29, 0.52)
Heme	Olanzapine	1	0	132	6	131	+Inf	(1.22, Inf+)
Musculoskeletal	Olanzapine	1	16	132	4	131	0.25	(0.06, 0.80)
Neuro	Aripiprazole	1	38	431	65	859	0.85	(0.55, 1.32)
Neuro/Fatigue	Olanzapine	1	104	636	150	1306	0.66	(0.50, 0.88)
Neuro/Movement Disorder	Olanzapine	1	115	636	102	1306	0.38	(0.29, 0.52)
Neuro/Movement Disorder/Akathisia	Aripiprazole	1	108	431	111	859	0.44	(0.33, 0.60)
Neuro/Movement Disorder/Akathisia	Olanzapine	2	266	768	203	1437	0.31	(0.25, 0.38)
Neuro/Movement Disorder/EPS	Aripiprazole	1	171	431	118	859	0.24	(0.18, 0.32)
Neuro/Movement Disorder/EPS	Olanzapine	4	414	808	371	1486	0.28	(0.23, 0.33)
Neuro/Movement Disorder/Gait	Olanzapine	1	20	636	22	1306	0.53	(0.27, 1.03)
Neuro/Sedation	Aripiprazole	1	32	431	43	859	0.66	(0.40, 1.09)
Neuro/Sedation	Olanzapine	3	220	669	340	1349	0.69	(0.56, 0.85)
Psychiatric	Olanzapine	1	15	636	13	1306	0.42	(0.18, 0.94)
Psychiatric/Agitation	Aripiprazole	1	30	431	53	859	0.88	(0.54, 1.45)
Psychiatric/Anxiety	Aripiprazole	1	50	431	108	859	1.10	(0.76, 1.60)
Psychiatric/Anxiety	Olanzapine	1	51	132	27	131	0.41	(0.22, 0.73)
Psychiatric/Lability	Olanzapine	1	7	132	10	131	1.55	(0.48, 5.45)
Psychiatric/Psychotic	Aripiprazole	1	70	431	156	859	1.14	(0.83, 1.58)
Psychiatric/Sleep	Aripiprazole	1	88	431	185	859	1.07	(0.80, 1.44)
Psychiatric/Sleep	Olanzapine	1	632	636	1122	1306	0.03	(0.01, 0.09)
Sweating	Olanzapine	1	84	636	89	1306	0.48	(0.35, 0.67)
Urinary	Olanzapine	1	39	636	47	1306	0.57	(0.36, 0.91)

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; OR = odds ratio

Table F6. Dementia—placebo controlled trials

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Anticholinergic Events	Olanzapine	1	12	90	60	178	3.29	(1.62, 7.17)	6
Appetite or Weight/Decrease	Aripiprazole	2	35	246	82	497	0.69	(0.43, 1.14)	NC
Appetite or Weight/Decrease	Olanzapine	2	15	141	32	363	0.75	(0.38, 1.56)	NC
Appetite or Weight/Decrease	Quetiapine	1	8	92	18	241	0.85	(0.34, 2.34)	NC
Appetite or Weight/Decrease	Risperidone	1	8	94	11	196	0.64	(0.23, 1.90)	NC
Appetite or Weight/Increase	Aripiprazole	2	10	223	23	472	1.02	(0.44, 2.49)	NC
Appetite or Weight/Increase	Olanzapine	3	6	326	34	482	4.69	(1.87, 14.14)	24
Appetite or Weight/Increase	Quetiapine	1	4	142	5	94	1.93	(0.40, 10.01)	NC
Appetite or Weight/Increase	Risperidone	2	5	236	14	281	3.40	(1.08, 12.75)	24
Cardiovascular	Aripiprazole	1	12	121	42	366	1.18	(0.58, 2.55)	NC
Cardiovascular	Olanzapine	5	9	440	40	778	2.33	(1.08, 5.61)	48
Cardiovascular	Quetiapine	3	15	254	29	355	1.08	(0.53, 2.30)	NC
Cardiovascular	Risperidone	6	34	1010	119	1757	2.08	(1.38, 3.22)	34
Cardiovascular/BP/Increase	Aripiprazole	1	5	102	4	106	0.76	(0.15, 3.65)	NC
Cardiovascular/BP/Increase	Olanzapine	1	1	67	2	137	0.98	(0.05, 58.55)	NC
Cardiovascular/BP/Increase	Quetiapine	1	0	20	1	20	+Inf	(0.03, Inf+)	NC
Cardiovascular/Rhythm	Aripiprazole	3	2	253	6	340	2.25	(0.38, 23.74)	NC
Cardiovascular/Rhythm	Olanzapine	2	6	209	3	237	0.37	(0.06, 1.85)	NC
Cardiovascular/Rhythm	Quetiapine	1	4	142	3	94	1.14	(0.16, 6.89)	NC
Cardiovascular/Rhythm	Risperidone	2	10	161	8	105	0.85	(0.24, 2.83)	NC
Constitutional/Fever or Infection	Aripiprazole	1	0	26	1	103	+Inf	(0.01, Inf+)	NC
Constitutional/Fever or Infection	Olanzapine	3	5	231	38	541	3.23	(1.23, 10.71)	34
Constitutional/Fever or Infection	Quetiapine	1	6	99	3	91	0.53	(0.08, 2.57)	NC
Constitutional/Fever or Infection	Risperidone	3	19	427	59	825	1.41	(0.80, 2.57)	NC
Death	Aripiprazole	3	3	253	8	340	2.37	(0.55, 14.18)	NC
Death	Olanzapine	2	4	232	2	278	0.48	(0.04, 3.62)	NC
Death	Quetiapine	2	7	241	5	185	0.91	(0.22, 3.41)	NC
Death	Risperidone	5	17	916	39	1561	1.19	(0.63, 2.31)	NC
Dermatologic	Aripiprazole	2	76	246	136	497	0.93	(0.65, 1.33)	NC
Dermatologic	Olanzapine	1	7	47	19	159	0.78	(0.29, 2.35)	NC
Dermatologic	Quetiapine	1	13	99	12	91	1.00	(0.39, 2.55)	NC
Dermatologic	Risperidone	2	82	333	133	629	1.24	(0.87, 1.79)	NC
Endocrine/Diabetes	Risperidone	1	5	238	4	235	0.81	(0.16, 3.80)	NC
Endocrine/Prolactin	Risperidone	1	0	238	0	235	NC	NC	NC

Table F6. Dementia—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Gastrointestinal	Aripiprazole	3	35	272	107	600	1.33	(0.85, 2.12)	NC
Gastrointestinal	Olanzapine	2	11	232	30	278	2.01	(0.93, 4.64)	NC
Gastrointestinal	Quetiapine	4	21	353	56	446	1.67	(0.95, 3.05)	NC
Gastrointestinal	Risperidone	2	66	312	40	252	0.54	(0.33, 0.87)	NC
HEENT	Aripiprazole	1	6	121	17	366	0.93	(0.34, 2.96)	NC
HEENT	Olanzapine	1	3	47	16	159	1.64	(0.44, 9.17)	NC
HEENT	Quetiapine	1	10	99	5	91	0.52	(0.13, 1.75)	NC
HEENT	Risperidone	2	27	333	80	629	1.27	(0.78, 2.12)	NC
HEENT/Decreased Salivation	Quetiapine	1	0	20	1	20	+Inf	(0.03, Inf+)	NC
HEENT/Eye	Aripiprazole	1	3	121	13	366	1.45	(0.39, 8.05)	NC
HEENT/Eye	Olanzapine	1	1	142	0	100	0.00	(0.00, 55.38)	NC
HEENT/Eye	Quetiapine	1	1	142	0	94	0.00	(0.00, 58.92)	NC
HEENT/Eye	Risperidone	2	19	312	20	252	1.10	(0.53, 2.26)	NC
HEENT/Increased Salivation	Aripiprazole	1	1	121	13	366	4.41	(0.65, 189.35)	NC
Heme	Aripiprazole	1	8	125	14	131	2.01	(0.73, 6.11)	NC
Heme	Olanzapine	1	1	142	1	100	1.42	(0.02, 112.58)	NC
Heme	Quetiapine	1	1	142	2	94	3.05	(0.16, 182.09)	NC
Heme	Risperidone	2	13	380	10	320	0.82	(0.32, 2.08)	NC
Infections	Aripiprazole	1	16	121	66	366	1.44	(0.78, 2.79)	NC
Infections	Olanzapine	1	5	90	10	178	1.01	(0.30, 3.90)	NC
Infections	Quetiapine	2	9	191	25	332	2.08	(0.88, 5.32)	NC
Infections	Risperidone	2	33	333	54	629	1.05	(0.64, 1.75)	NC
Liver Function Test Abnormality	Aripiprazole	1	1	102	0	106	0.00	(0.00, 37.53)	NC
Musculoskeletal	Olanzapine	1	3	90	0	178	0.00	(0.00, 1.21)	NC
Neuro	Aripiprazole	1	9	121	52	366	2.06	(0.96, 4.91)	NC
Neuro	Olanzapine	3	38	326	104	482	2.51	(1.62, 3.96)	8
Neuro	Quetiapine	4	23	353	36	446	1.83	(0.99, 3.45)	NC
Neuro	Risperidone	2	29	236	53	281	1.93	(1.12, 3.37)	12
Neuro/CVA	Aripiprazole	3	2	253	2	340	0.70	(0.05, 10.48)	NC
Neuro/CVA	Olanzapine	2	4	232	6	278	1.46	(0.33, 7.44)	NC
Neuro/CVA	Quetiapine	2	6	241	3	185	0.65	(0.10, 3.08)	NC
Neuro/CVA	Risperidone	4	8	753	24	1099	3.12	(1.32, 8.21)	53
Neuro/Fatigue	Aripiprazole	3	11	272	47	600	2.44	(1.19, 5.43)	22
Neuro/Fatigue	Olanzapine	3	9	326	36	482	2.37	(1.08, 5.75)	34
Neuro/Fatigue	Quetiapine	2	5	234	25	335	2.92	(1.03, 10.26)	34

Table F6. Dementia—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Neuro/Fatigue	Risperidone	2	4	236	20	281	3.56	(1.13, 14.96)	34
Neuro/Headache	Olanzapine	1	0	67	4	137	+Inf	(0.32, Inf+)	NC
Neuro/Headache	Risperidone	1	11	170	8	167	0.73	(0.25, 2.05)	NC
Neuro/Movement Disorder	Olanzapine	1	2	142	10	100	7.72	(1.59, 74.05)	15
Neuro/Movement Disorder	Quetiapine	1	2	142	5	94	3.91	(0.62, 41.89)	NC
Neuro/Movement Disorder	Risperidone	1	2	142	7	85	6.23	(1.15, 62.91)	16
Neuro/Movement Disorder/Akathisia	Olanzapine	1	0	142	1	100	+Inf	(0.04, Inf+)	NC
Neuro/Movement Disorder/Akathisia	Quetiapine	2	1	162	1	114	1.23	(0.02, 98.52)	NC
Neuro/Movement Disorder/Akathisia	Risperidone	1	0	142	0	85	NC	NC	NC
Neuro/Movement Disorder/EPS	Aripiprazole	4	16	374	39	706	1.29	(0.68, 2.57)	NC
Neuro/Movement Disorder/EPS	Olanzapine	1	2	142	18	100	15.21	(3.50, 138.55)	10
Neuro/Movement Disorder/EPS	Quetiapine	3	9	254	18	355	1.15	(0.46, 3.08)	NC
Neuro/Movement Disorder/EPS	Risperidone	5	31	916	130	1561	3.00	(1.96, 4.70)	20
Neuro/Movement Disorder/Gait	Aripiprazole	1	1	121	16	366	5.47	(0.83, 231.93)	NC
Neuro/Movement Disorder/Gait	Olanzapine	4	15	373	79	641	2.75	(1.52, 5.29)	21
Neuro/Movement Disorder/Gait	Quetiapine	3	6	333	18	426	2.36	(0.85, 7.59)	NC
Neuro/Movement Disorder/Gait	Risperidone	3	8	406	32	448	3.04	(1.32, 7.84)	33
Neuro/Movement Disorder/Tardive Dyskinesia	Olanzapine	1	4	142	3	100	1.07	(0.15, 6.46)	NC
Neuro/Movement Disorder/Tardive Dyskinesia	Quetiapine	1	4	142	2	94	0.75	(0.07, 5.36)	NC
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	4	14	713	4	949	0.31	(0.07, 1.03)	NC
Neuro/Pain	Aripiprazole	1	11	121	49	366	1.54	(0.76, 3.41)	NC
Neuro/Pain	Olanzapine	2	10	137	36	337	1.31	(0.60, 3.10)	NC
Neuro/Pain	Quetiapine	1	11	99	12	91	1.21	(0.46, 3.23)	NC
Neuro/Pain	Risperidone	1	13	163	33	462	0.89	(0.44, 1.89)	NC
Neuro/Sedation	Aripiprazole	4	22	374	116	706	2.62	(1.57, 4.54)	16
Neuro/Sedation	Olanzapine	5	25	440	158	778	4.58	(2.87, 7.55)	9
Neuro/Sedation	Quetiapine	4	18	353	84	446	5.16	(2.93, 9.51)	8
Neuro/Sedation	Risperidone	6	102	922	265	1260	2.33	(1.79, 3.05)	10
Psychiatric/Aggression	Olanzapine	1	1	94	14	204	6.82	(1.01, 292.81)	41
Psychiatric/Aggression	Risperidone	2	19	264	22	363	0.91	(0.45, 1.85)	NC
Psychiatric/Agitation	Aripiprazole	3	37	272	46	600	0.54	(0.32, 0.89)	NC
Psychiatric/Agitation	Olanzapine	4	36	373	76	641	1.19	(0.76, 1.90)	NC
Psychiatric/Agitation	Quetiapine	2	35	241	18	185	0.61	(0.31, 1.16)	NC

Table F6. Dementia—placebo controlled trials (continued)

Adverse Events	Drug	# of studies	Placebo		Atypicals		Pooled OR	95% CI	NNH
			# adverse events	sample size	# adverse events	sample size			
Psychiatric/Agitation	Risperidone	5	102	807	120	1145	0.84	(0.62, 1.14)	NC
Psychiatric/Anxiety	Olanzapine	4	19	373	40	641	1.04	(0.57, 1.95)	NC
Psychiatric/Anxiety	Quetiapine	1	3	142	0	94	0.00	(0.00, 3.65)	NC
Psychiatric/Anxiety	Risperidone	2	12	236	20	281	0.89	(0.39, 2.12)	NC
Psychiatric/Cognitive	Aripiprazole	1	0	26	3	103	+Inf	(0.10, Inf+)	NC
Psychiatric/Cognitive	Olanzapine	2	3	232	15	278	4.00	(1.08, 22.38)	38
Psychiatric/Cognitive	Quetiapine	1	1	142	0	94	0.00	(0.00, 58.92)	NC
Psychiatric/Cognitive	Risperidone	1	1	142	1	85	1.67	(0.02, 132.68)	NC
Psychiatric/Depression	Olanzapine	2	4	232	16	278	3.05	(0.94, 13.04)	NC
Psychiatric/Depression	Quetiapine	1	2	142	2	94	1.52	(0.11, 21.30)	NC
Psychiatric/Depression	Risperidone	1	2	142	0	85	0.00	(0.00, 8.90)	NC
Psychiatric/Psychotic	Olanzapine	3	14	326	62	482	2.81	(1.49, 5.64)	18
Psychiatric/Psychotic	Quetiapine	1	3	142	0	94	0.00	(0.00, 3.65)	NC
Psychiatric/Psychotic	Risperidone	2	13	236	32	281	1.35	(0.65, 2.96)	NC
Psychiatric/Sleep	Olanzapine	3	13	326	30	482	1.50	(0.73, 3.26)	NC
Psychiatric/Sleep	Quetiapine	1	5	142	5	94	1.54	(0.34, 6.88)	NC
Psychiatric/Sleep	Risperidone	2	10	236	15	281	1.17	(0.46, 3.09)	NC
Pulmonary	Aripiprazole	1	3	102	6	106	1.97	(0.41, 12.54)	NC
Pulmonary	Olanzapine	1	3	94	0	204	0.00	(0.00, 1.10)	NC
Pulmonary	Risperidone	1	3	94	6	196	0.96	(0.20, 6.05)	NC
Trauma	Aripiprazole	4	70	374	128	706	0.93	(0.65, 1.33)	NC
Trauma	Olanzapine	5	50	440	114	778	1.31	(0.89, 1.96)	NC
Trauma	Quetiapine	4	137	353	167	446	0.76	(0.53, 1.09)	NC
Trauma	Risperidone	5	289	807	403	1145	0.79	(0.63, 0.99)	19
Urinary	Aripiprazole	3	44	348	115	603	1.37	(0.92, 2.09)	NC
Urinary	Olanzapine	1	1	94	19	204	9.51	(1.47, 401.07)	36
Urinary	Quetiapine	2	12	191	44	332	2.37	(1.16, 5.15)	16
Urinary	Risperidone	4	71	665	164	1060	1.55	(1.13, 2.13)	21

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; NNH = number needed to harm; OR = odds ratio

Table F7. Dementia—active controlled trials versus acetylcholinesterase inhibitors

Adverse Events	Drug	# of studies	Acetylcholinesterase Inhibitor		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Risperidone	1	0	14	0	13	NC	NC
Gastrointestinal	Risperidone	1	10	14	2	13	0.10	(0.01, 0.78)
Neuro/Fatigue	Risperidone	1	2	14	1	13	1.09	(0.01, 92.68)
Neuro/Movement Disorder/EPS	Risperidone	1	0	14	2	13	+Inf	(0.03, Inf+)
Neuro/Sedation	Risperidone	1	0	14	4	13	+Inf	(0.88, Inf+)
Psychiatric/Agitation	Risperidone	1	1	14	1	13	+Inf	(0.03, Inf+)

CI = confidence interval; NC = not calculated; OR = odds ratio

Table F8. Dementia—active controlled trials versus benzodiazepines

Adverse Events	Drug	# of studies	Benzodiazepine		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Cardiovascular	Olanzapine	1	0	68	2	137	+Inf	(0.09, Inf+)
Cardiovascular/BP/Increase	Olanzapine	1	2	68	2	137	0.49	(0.03, 6.91)
Cardiovascular/Rhythm	Olanzapine	1	0	68	3	137	+Inf	(0.20, Inf+)
Neuro/Headache	Olanzapine	1	1	68	4	137	2.01	(0.19, 100.69)
Neuro/Sedation	Olanzapine	1	7	68	5	137	0.33	(0.08, 1.27)
Trauma	Olanzapine	1	3	68	3	137	0.49	(0.06, 3.74)

CI = confidence interval; OR = odds ratio

Table F9. Dementia—active controlled trials versus conventionals

Adverse Events	Drug	# of studies	Conventional		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Olanzapine	1	3	28	4	30	1.28	(0.19, 9.61)
Appetite or Weight/Increase	Olanzapine	3	19	221	28	223	1.53	(0.79, 3.03)
Appetite or Weight/Increase	Risperidone	1	0	20	0	20	NC	NC
Cardiovascular	Olanzapine	1	2	173	6	173	3.06	(0.54, 31.45)
Cardiovascular/BP/Decrease	Olanzapine	1	7	20	2	20	0.11	(0.00, 1.01)
Cardiovascular/BP/Decrease	Risperidone	1	7	20	4	20	0.47	(0.08, 2.36)
Cardiovascular/BP/Increase	Quetiapine	1	1	11	1	11	1.00	(0.01, 86.25)
Cardiovascular/Rhythm	Olanzapine	2	6	48	3	50	0.46	(0.07, 2.29)
Cardiovascular/Rhythm	Risperidone	1	5	20	2	20	0.17	(0.00, 1.80)
Constitutional/Fever or Infection	Olanzapine	1	3	173	0	173	0.00	(0.00, 2.41)
Death	Olanzapine	1	6	173	4	173	0.66	(0.13, 2.84)
Dermatologic	Olanzapine	1	12	28	7	30	0.41	(0.11, 1.43)
Endocrine/Diabetes	Olanzapine	2	2	193	3	193	1.50	(0.17, 18.14)
Endocrine/Diabetes	Risperidone	1	0	20	0	20	NC	NC
Gastrointestinal	Olanzapine	3	64	221	24	223	0.14	(0.06, 0.30)
Gastrointestinal	Quetiapine	1	0	11	1	11	+Inf	(0.03, Inf+)
Gastrointestinal	Risperidone	2	10	49	6	49	0.43	(0.10, 1.65)
HEENT/Decreased Salivation	Olanzapine	2	10	48	3	50	0.25	(0.04, 1.05)
HEENT/Decreased Salivation	Risperidone	1	6	20	0	20	0.00	(0.00, 0.72)
HEENT/Increased Salivation	Olanzapine	1	7	28	4	30	0.47	(0.09, 2.14)
Infections	Quetiapine	1	1	11	0	11	0.00	(0.00, 39.00)
Neuro	Olanzapine	2	20	48	15	50	0.55	(0.20, 1.47)
Neuro	Risperidone	1	3	20	0	20	0.00	(0.00, 2.34)
Neuro/Fatigue	Olanzapine	2	22	48	18	50	0.42	(0.11, 1.49)
Neuro/Fatigue	Risperidone	1	0	20	2	20	+Inf	(0.03, Inf+)
Neuro/Movement Disorder	Olanzapine	1	18	28	19	30	0.96	(0.29, 3.20)
Neuro/Movement Disorder/Akathisia	Olanzapine	2	6	48	5	50	0.57	(0.10, 2.76)
Neuro/Movement Disorder/Akathisia	Risperidone	1	0	20	0	20	NC	NC
Neuro/Movement Disorder/EPS	Olanzapine	2	24	48	17	50	0.37	(0.12, 1.10)
Neuro/Movement Disorder/EPS	Quetiapine	1	2	11	0	11	0.00	(0.00, 5.24)
Neuro/Movement Disorder/EPS	Risperidone	1	4	20	2	20	0.23	(0.00, 2.65)

Table F9. Dementia—active controlled trials versus conventionals (continued)

Adverse Events	Drug	# of studies	Conventional		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Neuro/Sedation	Olanzapine	3	67	221	64	223	0.90	(0.57, 1.42)
Neuro/Sedation	Risperidone	3	25	163	18	164	0.68	(0.33, 1.36)
Neuro/Sensory	Olanzapine	1	2	28	2	30	0.93	(0.06, 13.69)
Psychiatric/Apathy	Olanzapine	1	16	28	10	30	0.38	(0.11, 1.23)
Psychiatric/Cognitive	Olanzapine	1	49	28	53	30	NC	NC
Psychiatric/Depression	Olanzapine	1	20	28	17	30	0.53	(0.15, 1.77)
Psychiatric/Irritability	Olanzapine	1	23	28	24	30	0.87	(0.18, 3.97)
Psychiatric/Sexual	Olanzapine	1	0	20	0	20	NC	NC
Psychiatric/Sexual	Risperidone	1	0	20	1	20	NC	NC
Psychiatric/Sexual/Decreased Function	Olanzapine	1	3	28	4	30	1.28	(0.19, 9.61)
Psychiatric/Sleep	Olanzapine	2	23	48	34	50	NC	NC
Psychiatric/Sleep	Risperidone	1	0	20	1	20	NC	NC
Sweating	Olanzapine	1	4	28	5	30	1.20	(0.23, 6.79)
Trauma	Olanzapine	1	13	173	1	173	0.07	(0.00, 0.49)
Urinary	Olanzapine	2	12	201	12	203	0.90	(0.29, 2.80)
Urinary	Risperidone	1	0	29	1	29	+Inf	(0.03, Inf+)

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; OR = odds ratio

Table F10. Dementia—active controlled trials versus SRI

Adverse Events	Drug	# of studies	SRI		Atypicals		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Cardiovascular/BP/Decrease	Risperidone	1	0	53	1	50	+Inf	(0.03, Inf+)
Constitutional/Fever or Infection	Risperidone	1	0	53	2	50	+Inf	(0.20, Inf+)
Endocrine	Risperidone	1	1	53	0	50	0.00	(0.00, 41.34)
Gastrointestinal	Risperidone	1	1	53	2	50	2.15	(0.11, 130.24)
Infections	Risperidone	1	2	53	0	50	0.00	(0.00, 5.63)
Liver Function Test Abnormality	Risperidone	1	0	53	1	50	+Inf	(0.03, Inf+)
Neuro	Risperidone	1	1	53	0	50	0.00	(0.00, 41.34)
Neuro/Movement Disorder/EPS	Risperidone	1	1	53	3	50	3.28	(0.25, 177.53)
Neuro/Movement Disorder/Gait	Risperidone	1	1	53	3	50	3.28	(0.25, 177.53)
Neuro/Sedation	Risperidone	1	1	53	0	50	0.00	(0.00, 41.34)
Psychiatric/Agitation	Risperidone	1	12	53	7	50	0.56	(0.17, 1.72)
Psychiatric/Depression	Risperidone	1	1	53	0	50	0.00	(0.00, 41.34)
Psychiatric/Psychotic	Risperidone	1	1	53	1	50	1.06	(0.01, 84.88)
Psychiatric/Serious	Risperidone	1	2	53	3	50	1.62	(0.18, 20.19)
Psychiatric/Suicide Attempt	Risperidone	1	0	53	1	50	+Inf	(0.03, Inf+)
Trauma	Risperidone	1	1	53	0	50	0.00	(0.00, 41.34)

CI = confidence interval; OR = odds ratio

Table F11. Dementia—head-to-head trials

Adverse Events			Risperidone			Olanzapine or Quetiapine		Pooled OR	95% CI
	Risperidone	Olanzapine or Quetiapine	# of studies	# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Risperidone	Olanzapine	1	11	196	13	204	1.14	(0.46, 2.90)
Appetite or Weight/Increase	Risperidone	Olanzapine	3	14	301	27	324	1.87	(0.92, 3.95)
Appetite or Weight/Increase	Risperidone	Quetiapine	1	8	85	5	94	0.54	(0.13, 1.97)
Cardiovascular	Risperidone	Olanzapine	2	16	281	13	304	0.75	(0.33, 1.70)
Cardiovascular	Risperidone	Quetiapine	2	4	119	6	132	1.38	(0.31, 6.89)
Cardiovascular/BP/Decrease	Risperidone	Olanzapine	1	4	20	2	20	0.23	(0.00, 2.65)
Cardiovascular/Rhythm	Risperidone	Olanzapine	3	3	124	2	140	0.92	(0.07, 12.95)
Cardiovascular/Rhythm	Risperidone	Quetiapine	1	1	85	3	94	2.75	(0.22, 147.08)
Constitutional/Fever or Infection	Risperidone	Olanzapine	1	0	196	2	204	+Inf	(0.18, Inf+)
Death	Risperidone	Olanzapine	1	1	85	1	100	0.85	(0.01, 67.39)
Death	Risperidone	Quetiapine	2	1	119	3	132	2.75	(0.22, 147.08)
Dermatologic	Risperidone	Olanzapine	1	0	19	1	20	+Inf	(0.02, Inf+)
Endocrine/Diabetes	Risperidone	Olanzapine	1	0	20	1	20	+Inf	(0.03, Inf+)
Gastrointestinal	Risperidone	Olanzapine	2	7	105	9	120	1.42	(0.42, 5.18)
Gastrointestinal	Risperidone	Quetiapine	2	8	119	3	132	0.31	(0.05, 1.37)
HEENT/Decreased Salivation	Risperidone	Olanzapine	1	0	20	0	20	NC	NC
HEENT/Eye	Risperidone	Olanzapine	1	0	85	0	100	NC	NC
HEENT/Eye	Risperidone	Quetiapine	2	2	119	0	132	0.00	(0.00, 4.73)
Heme	Risperidone	Olanzapine	1	2	85	1	100	0.42	(0.01, 8.22)
Heme	Risperidone	Quetiapine	1	2	85	2	94	0.90	(0.06, 12.71)
Musculoskeletal	Risperidone	Quetiapine	1	5	34	0	38	0.00	(0.00, 0.92)
Neuro	Risperidone	Olanzapine	3	53	301	81	324	1.54	(1.02, 2.34)
Neuro	Risperidone	Quetiapine	1	22	85	19	94	0.73	(0.34, 1.55)
Neuro/CVA	Risperidone	Olanzapine	2	2	104	4	120	1.75	(0.25, 19.64)
Neuro/CVA	Risperidone	Quetiapine	2	2	119	2	132	0.90	(0.06, 12.71)
Neuro/Fatigue	Risperidone	Olanzapine	3	22	301	18	324	0.80	(0.39, 1.61)
Neuro/Fatigue	Risperidone	Quetiapine	2	5	119	8	132	1.47	(0.41, 5.88)
Neuro/Movement Disorder	Risperidone	Olanzapine	1	7	85	10	100	1.24	(0.40, 4.02)
Neuro/Movement Disorder	Risperidone	Quetiapine	1	7	85	5	94	0.63	(0.15, 2.40)
Neuro/Movement Disorder/Akathisia	Risperidone	Olanzapine	2	0	105	2	120	+Inf	(0.02, Inf+)
Neuro/Movement Disorder/Akathisia	Risperidone	Quetiapine	1	0	85	1	94	+Inf	(0.02, Inf+)
Neuro/Movement Disorder/EPS	Risperidone	Olanzapine	3	19	124	18	140	0.84	(0.38, 1.82)
Neuro/Movement Disorder/EPS	Risperidone	Quetiapine	2	20	119	3	132	0.12	(0.02, 0.41)

Table F11. Dementia—head-to-head trials (continued)

Adverse Events			# of studies	Risperidone		Olanzapine or Quetiapine		Pooled OR	95% CI
	Risperidone	Olanzapine or Quetiapine		# adverse events	sample size	# adverse events	sample size		
Neuro/Movement Disorder/Gait	Risperidone	Olanzapine	3	22	300	26	324	1.13	(0.60, 2.16)
Neuro/Movement Disorder/Gait	Risperidone	Quetiapine	1	1	85	3	94	2.75	(0.22, 147.08)
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	Olanzapine	1	3	85	3	100	0.85	(0.11, 6.49)
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	Quetiapine	1	3	85	2	94	0.60	(0.05, 5.34)
Neuro/Sedation	Risperidone	Olanzapine	5	63	391	89	428	1.40	(0.96, 2.05)
Neuro/Sedation	Risperidone	Quetiapine	2	17	119	32	132	1.93	(0.97, 3.97)
Psychiatric/Aggression	Risperidone	Olanzapine	1	13	196	14	204	1.04	(0.44, 2.47)
Psychiatric/Agitation	Risperidone	Olanzapine	2	35	281	44	304	1.22	(0.73, 2.04)
Psychiatric/Agitation	Risperidone	Quetiapine	1	5	85	11	94	2.11	(0.64, 8.11)
Psychiatric/Anxiety	Risperidone	Olanzapine	2	20	281	19	304	0.90	(0.44, 1.83)
Psychiatric/Anxiety	Risperidone	Quetiapine	1	0	85	0	94	NC	NC
Psychiatric/Cognitive	Risperidone	Olanzapine	1	1	85	5	100	4.39	(0.48, 211.54)
Psychiatric/Cognitive	Risperidone	Quetiapine	1	1	85	0	94	0.00	(0.00, 35.27)
Psychiatric/Depression	Risperidone	Olanzapine	1	0	85	4	100	+Inf	(0.57, Inf+)
Psychiatric/Depression	Risperidone	Quetiapine	1	0	85	2	94	+Inf	(0.17, Inf+)
Psychiatric/Psychotic	Risperidone	Olanzapine	2	32	281	52	304	1.70	(1.02, 2.85)
Psychiatric/Psychotic	Risperidone	Quetiapine	2	1	119	0	132	0.00	(0.00, 34.89)
Psychiatric/Sexual	Risperidone	Olanzapine	1	1	20	0	20	NC	NC
Psychiatric/Sleep	Risperidone	Olanzapine	3	16	301	19	324	1.19	(0.56, 2.57)
Psychiatric/Sleep	Risperidone	Quetiapine	1	4	85	5	94	1.14	(0.24, 5.93)
Pulmonary	Risperidone	Olanzapine	1	6	196	0	204	0.00	(0.00, 0.80)
Trauma	Risperidone	Olanzapine	3	30	300	50	324	1.64	(0.98, 2.76)
Trauma	Risperidone	Quetiapine	2	10	119	12	132	1.09	(0.41, 2.94)
Urinary	Risperidone	Olanzapine	1	25	196	19	204	0.70	(0.35, 1.38)
Urinary	Risperidone	Quetiapine	1	0	34	2	38	+Inf	(0.17, Inf+)

CI = confidence interval; HEENT = head, eye, ear, nose, and throat; NC = not calculated; OR = odds ratio