Effective Health Care Program

Comparative Effectiveness Review
Number 33

Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults

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Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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

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

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail 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 e-mail to epc@ahrq.hhs.gov.

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Executive Summary

Background

Major depressive disorder (MDD) is common and costly. Over the course of a year, between 13.1 million and 14.2 million people will experience MDD. Approximately half of these people seek help for this condition, and only 20 percent of those receive adequate treatment. For those who do initiate treatment for their depression, approximately 50 percent will not adequately respond following acute-phase treatment; this refractory group has considerable clinical and research interest. Patients with only one prior treatment failure are sometimes included in this group, but patients with two or more prior treatment failures are a particularly important and poorly understood group and are considered to have treatment-resistant depression (TRD). These TRD patients represent a complex population with a disease that is difficult to manage.

Patients with TRD incur the highest direct and indirect medical costs among those with MDD. These costs increase with the severity of TRD. Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than six times the mean total costs of depressed patients who are not treatment resistant. After considering both medical and disability claims from an employer's perspective, one study found that TRD employees cost $14,490 per employee per year, whereas the cost for non-TRD employees was $6,665 per employee per year.

Given the burden of TRD generally, the uncertain prognosis of the disorder, and the high costs of therapy, clinicians and patients alike need clear evidence to guide their treatment decisions. The choices are wide ranging, include both pharmacologic and nonpharmacologic interventions, and are fraught with incomplete, potentially conflicting evidence. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for patients with TRD. Antidepressant medications, which are the most commonly used intervention, have decreasing efficacy for producing remission after patients have experienced two treatment failures. Such drugs also often have side effects, sometimes minor but sometimes quite serious. For these reasons, clinicians often look for alternative strategies for their TRD patients.

This review from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (EPC) provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments as therapies for patients with TRD: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT).

The core patient population of interest was patients with MDD who met our definition of TRD: failure to respond following two or more adequate antidepressant treatments. We also included TRD studies in which the patient population could include a "mix" of up to 20 percent of patients with bipolar disorder (i.e., 80 percent or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations.

We structured our review to maintain our focus on study populations meeting our TRD definition (≥2 antidepressant failures) while not excluding potentially relevant evidence. We identified different tiers of TRD-related studies to use in our analytic strategy:

- **Tier 1** Evidence (TRD as defined in this report): studies in which patients specifically had two or more prior treatment failures with medications.
- **Tier 2** Evidence: studies in which patients had one or more prior treatment failures.
- **Tier 3** Evidence: studies in which the number of prior failed treatments was not specified but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures; these data have probable relevance to TRD. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

This comparative effectiveness review is intended to help various decisionmakers come to informed choices about the use of nonpharmacologic interventions for TRD in adults. Our principal goal is to summarize comparative data on the efficacy, effectiveness, and harms of ECT, rTMS, VNS, and CBT/IPT in patients with TRD. Comparisons of these nonpharmacologic therapies are our main interest. However, because treatment decisions made by patients with TRD and their clinicians are not limited to nonpharmacologic options, we also compare nonpharmacologic options with pharmacologic ones. We address the following six Key Questions (KQs) as specified by the Agency for Healthcare Research and Quality (AHRQ). "Trials" in these KQs refers to treatment attempts, not experimental studies.

- KQ 1a. For adults with TRD (defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- KQ 1b. How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?
- KQ 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?
- KQ 3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?
- KQ 4. For adults with TRD, do nonpharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.
- KQ 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations:
    - Elderly or very elderly patients; other demographic groups (defined by age, ethnic or racial groups, and sex)?
    - Patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer)?
- KQ 6. For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

We searched MEDLINE, Embase, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts. We searched for systematic reviews, clinical controlled trials, meta-analyses, and nonexperimental studies in which the investigator did not assign group allocation. Sources were searched from 1980 through November 18, 2010. AHRQ Scientific Resource Center (SRC) staff contacted device manufacturers and invited them to submit dossiers, including citations. The SRC also provided our EPC with other relevant data that may not have been captured in the literature search.

For efficacy and effectiveness (KQs 1 and 2), we first focused on head-to-head randomized controlled trials (RCTs) comparing one intervention with another. When sufficient head-to-head evidence was unavailable, we evaluated indirect evidence: nonpharmacologic interventions versus placebo- or sham-controlled evidence or "treatment as usual" controls. For KQs 3, 4, 5, and 6, we examined data from both experimental and observational studies (generally prospective cohort studies). We did not formally distinguish efficacy from effectiveness trials.

We rated the quality of individual studies as good, fair, or poor; only good or fair studies are included in these analyses. We evaluated the strength of the various bodies of evidence using principles stated in the AHRQ Methods Guide for Comparative Effectiveness Reviews, which grades strength as high, moderate, low, or insufficient. We evaluated the applicability of the body of evidence using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting.

Throughout this report we synthesized the literature qualitatively. If data were sufficient, we conducted meta-analyses of data for comparisons involving trials that were fairly homogenous in study populations, treatment intervention, and outcome assessments. Given our focus on Tier 1 (TRD) studies, for each KQ we first present an overview of the particular comparison, including the strength of evidence findings for the Tier 1 studies. This summary does not present detailed findings from the Tier 2 and Tier 3 studies. The results chapter of the full report presents those data in greater detail.

Results: Overview

From a total of 2,754 citations retrieved, we ultimately identified 79 good-, fair-, or poor-quality articles in this review; they represent 64 studies. Of these studies, there were 17 head-to-head RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a nonpharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTS of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RCTs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). We excluded 8 studies (8 articles) because of poor quality. We present evidence that allows comparison of the four nonpharmacologic treatments of interest (ECT, rTMS, VNS, and psychotherapy) stratified by tiers of evidence.

Comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy. Many clinical questions about efficacy and effectiveness remain unanswered. The text below presents our principal results; summary tables (A–J) document Tier 1 TRD findings for major comparisons and outcomes for each key question, give the overall strength of evidence for that comparison, and outline key findings. We report first on direct evidence (head-to-head comparisons) and then on indirect evidence (e.g., trials using controls). If a specific comparison did not involve a Tier 1 population but did have trials conducted in a Tier 2 and/or Tier 3

population, we have listed it in this table, noted "No eligible studies identified," and added a footnote indicating the presence of at least one such study.

The greatest volume of evidence is for ECT and rTMS; however, the direct comparative evidence about even these treatments is quite limited. Available indirect evidence primarily involves rTMS; a little information is available on VNS and psychotherapy (chiefly for efficacy and adverse events), and no available indirect evidence involves ECT. Given the limited number of Tier 1 studies incomplete reporting on the number of failed treatment attempts, we were unable to stratify our outcomes by the number of treatment failures within Tier 1.

Table A. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a, comparative efficacy of nonpharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	42	Low	1 fair trial: both ECT and rTMS improved symptom severity but did not differ significantly.
ECT vs. rTMS	Response rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT vs. rTMS	Remission rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT plus rTMS vs. ECT	Change in depressive severity	22	Low	1 fair trial: both ECT and ECT plus rTMS improved symptom severity but did not differ significantly.
ECT plus rTMS vs. ECT	Response rate	0	NA	No eligible studies identified. ‡
ECT plus rTMS vs. ECT	Remission rate	22	Low	1 fair trial: ECT and ECT plus rTMS did not differ significantly.
ECT vs. sham	Change in depressive severity	0	NA	No eligible studies identified. ‡
ECT vs. sham	Response rate	0	NA	No eligible studies identified. ‡
ECT vs. sham	Remission rate	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Change in depressive severity	497	High	7 trials (3 good, 4 fair): rTMS had a significantly greater decrease in depressive severity than sham. 4 fair trials: rTMS had nonsignificantly greater decrease in depressive severity than sham. 2 fair trials: rTMS had greater decrease than sham but significance NR. 1 fair trial: rTMS did not significantly differ from sham.
rTMS vs. sham	Response rate	471	High	4 trials (3 good, 1 fair): rTMS had a significantly higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly higher response rate than sham. 6 fair trials: rTMS had a higher response rate than sham, but significance NR. 1 fair trial: rTMS did not clearly differ from sham, but significance NR.
rTMS vs. sham	Remission rate	223	Moderate	3 trials (2 good, 1 fair): rTMS had significantly greater remission rate than sham. 1 fair trial: rTMS had a greater remission rate than sham but significance NR.
VNS vs. sham	Change in depressive severity	235	Low	1 good trial: VNS and sham did not differ significantly.
VNS vs. sham	Response rate	235	Low	1 good trial: VNS and sham did not differ significantly.
Psychotherapy vs. control	Change in depressive severity	0	NA	No eligible studies identified. ‡

Table A. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a, comparative efficacy of nonpharmacologic treatments (continued)

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
Psychotherapy vs. control	Response rate	0	NA	No eligible studies identified. ‡
Psychotherapy vs. control	Remission rate	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 or Tier 3 study addressed this comparison.

Table B. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 1b, comparative efficacy of nonpharmacologic and pharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. pharmacotherapy	Change in depressive severity	39	Low	1 fair trial: ECT had significantly greater improvement in symptom severity than pharmacotherapy.
ECT vs. pharmacotherapy	Response rate	39	Low	1 fair trial: ECT had significantly greater response rates than pharmacotherapy.
Psychotherapy vs. pharmacotherapy	Change in depressive severity	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Response rate	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Remission rate	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table C. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 2, comparative efficacy for maintaining remission

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Maintenance of remission	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Maintenance of remission	68	Insufficient	3 fair trials: no significant differences in maintenance of remission; however, small sample sizes in two of the studies and the presence of a co-intervention in the third study make results difficult to interpret.
CBT vs. usual care	Maintenance of remission	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table D. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 3, comparative efficacy for particular symptom subtypes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table E. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4a, impact of nonpharmacologic interventions on cognitive functioning

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Cognitive functioning	72	Insufficient	1 fair trial and 1 fair cohort study: Some evidence suggests no difference between treatments, whereas some evidence suggests ECT may have deleterious impact on cognitive functioning compared with rTMS (1 study: significant effect on 1-week recall; both studies: nonsignificant effect on all other measures).
ECT vs. ECT + rTMS	Cognitive functioning	22	Insufficient	1 fair trial: no significant differences in a single item measure on memory problems.
rTMS vs. sham	Cognitive functioning	161	Insufficient	4 trials (1 good, 3 fair): Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham (2 trials: significant differences in memory, verbal fluency; all other findings nonsignificant or significance not reported).

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.

Table F. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4b, specific adverse events

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Adverse events	0	NA	No eligible studies identified. ‡
ECT vs. ECT + rTMS	Adverse events	22	Low	1 fair trial: no significant differences in specific adverse events
rTMS vs. sham	Adverse events	68	Low	1 good trial: rTMS resulted in significantly more scalp pain at the stimulation site than sham.
VNS vs. sham	Adverse events	235	Low	1 fair trial: Some differences in specific adverse events reported (*P* = NR)

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table G. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4c, withdrawals due to adverse event

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Withdrawals	30	Low	1 fair cohort study: no difference in withdrawals between ECT and rTMS groups (*P* = NR).
ECT vs. sham	Withdrawals	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Withdrawals	337	Insufficient	7 trials (1 good, 6 fair): trials showed mixed results about withdrawals attributed to adverse events.
VNS vs. sham	Withdrawals	235	Low	1 good trial: VNS had greater withdrawals attributed to adverse events than sham (significance NR).
CBT vs. usual care	Withdrawals	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table H. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4d, adherence as measured by overall withdrawals

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Overall withdrawals	72	Low	1 fair trial and 1 fair cohort study: studies showed more withdrawals in the ECT group compared with rTMS (*P* = NR).
ECT vs. sham	Overall withdrawals	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Overall withdrawals	325	Insufficient	8 fair trials: trials showed mixed results about withdrawals.
CBT vs. usual care	Overall withdrawals	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table I. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 5, efficacy and harms for selected populations

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
rTMS vs. sham	Changes in depressive severity	34	Low	1 fair trial: rTMS produced better outcome than sham in young adult population (ages 18–37).
rTMS vs. sham	Changes in depressive severity	20	Low	1 fair trial: rTMS produced better outcome than sham in older adults with post-stroke depression.
rTMS vs. sham	Response	34	Low	1 fair trial: rTMS produces better response rates than sham in young adult population (ages 18–37).
rTMS vs. sham	Response	20	Low	1 fair trial: no difference between rTMS and sham for older adults with post-stroke depression.
rTMS vs. sham	Remission	20	Low	1 fair trial: no difference between rTMS and sham in older adults with post-stroke depression.

rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.

Table J. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 6, health-related outcomes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. ECT + rTMS	Health-related outcomes	22	Low	1 fair trial: There were no differences between groups in improvements in daily functioning.
rTMS vs. sham	Health-related outcomes	60	Low	1 fair trail: low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham.
VNS vs. sham	Health-related outcomes	214	Low	1 fair trial: VNS and sham groups did not differ significantly in daily functioning.
CBT/DBT vs. control	Health-related outcomes	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus
*Strength of evidence is based on the on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions (KQ 1a)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD is limited to two fair trials (both in MDD-only populations). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

Indirect Evidence

We identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS, or psychotherapy, with a control or sham procedure in Tier 1 populations. We identified no eligible ECT versus control studies. The number of these trials with the same or similar control group was very small, so we could not pool them quantitatively. We could, however, assess the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than six times as likely to achieve remission as those receiving the sham.

In the only other Tier 1 comparison, one good-quality VNS versus sham control trial (a mixed MDD/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies (KQ 1b)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) for Tier 1 trials is limited to one fair trial (a mixed MDD/bipolar population). ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71 percent vs. 28 percent) than medications (low strength of evidence).

Indirect Evidence

Indirect evidence about procedures or psychotherapy (vs. sham or nonpharmacologic controls) was presented above as part of KQ 1.

We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, we found no comparable, common control groups (i.e., patients not receiving a mood-related medication) to allow such comparisons.

Instead, we determined mean average outcomes for pharmacologic treatments.

- For switching strategies, mean pharmacologic response rates averaged 39.8 percent (95% CI, 30.7% to 48.9%) and mean remission rates averaged 22.3 percent (95% CI, 16.2% to 28.4%).
- For augmentation, mean response rates averaged 38.1 percent (31.0% to 45.3%) and mean remission rates averaged 27.2 percent (20.4% to 34.0%).
- For maintenance strategies, mean response rates averaged 27.3 percent (19.8% to 34.8%) and mean remission rates averaged 16.8 percent (13.5% to 20.2%).

Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should be compared to nonpharmacologic outcomes only with caution.

Maintenance of Remission or Prevention of Relapse (KQ 2)

Direct Evidence

With respect to maintaining remission (or preventing relapse), we had no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence

Three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in two of the three studies, and patients in the third received a co-intervention providing insufficient evidence for a conclusion. We had no eligible studies for ECT, VNS, or psychotherapy.

Efficacy of Nonpharmacologic Interventions for Patients With Different Symptomatology (KQ 3)

Direct Evidence

We identified no Tier 1 trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

Indirect Evidence

We identified no studies testing either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

Safety, Adverse Events, and Adherence (KQ 4)

Direct Evidence

In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. For just this set of analyses, we examined both clinical trials and cohort studies, and we focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

Cognitive Functioning

For Tier 1 studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence). No differences between groups on a single-item measure of cognitive functioning were found in a study comparing ECT with ECT and rTMS (insufficient strength of evidence).

Specific Adverse Events

One Tier 1 study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence).

Withdrawals

We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).

Evidence for ECT compared with rTMS indicated higher rates of overall withdrawals in the ECT compared to the rTMS group (*P* = NR; low strength of evidence).

Indirect Evidence

We attempted to include data from the same types of studies and for the same outcomes as for direct evidence. We identified no studies comparing ECT versus control.

Cognitive Functioning

Mixed evidence on cognitive functioning in rTMS versus sham was insufficient evidence to draw a conclusion (insufficient strength of evidence).

Specific Adverse Events

rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence).

Some differences in the frequency of specific adverse events were seen when comparing VNS and sham groups, but the significance of the findings was not reported (*P* = NR) (low strength of evidence).

Withdrawals

Findings were mixed in Tier 1 studies as to whether rTMS groups had greater rates of withdrawals (overall and due to adverse events) than groups receiving sham procedures (insufficient evidence for both).

Withdrawals attributable to adverse events were higher in the VNS group compared with sham (low strength of evidence).

No Tier 1 studies reported on withdrawals for CBT groups versus those receiving some form of usual care.

Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups (KQ 5)

Direct Evidence

We found no studies (in any tier) directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

Indirect Evidence

Two Tier 1 trials compared rTMS with sham. All findings provided low strength of evidence. For young adults (ages 18–37), one trial found that rTMS produced a greater decrease in depressive severity and a greater response rate than sham. A second trial, conducted in older adults with post-stroke depression, found that rTMS produced a greater decrease in depressive severity and a greater response rate but no difference in remission rates compared with a sham control.

Health-Related Outcomes of Nonpharmacologic Treatments (KQ 6)

Direct Evidence

With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

Indirect Evidence

Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

Applicability

For the limited amount and low strength of evidence available, the data for Tier 1 (TRD) is generally applicable to TRD populations. Populations enrolled in these trials appeared representative of our target population. Studied interventions were comparable to those in routine use, though dose and duration of nonpharmacalogic treatment often varied between studies.

Measured outcomes on the whole reflected the most important clinical outcomes for depression measures, although reporting was inconsistent; outcomes for the other key questions were much more restricted. Followup periods were generally shorter than desirable, but most

were sufficient to measure an initial acute-phase treatment response. Study settings were a mixture of inpatient and outpatient, because ECT is generally an inpatient procedure and the others are generally outpatient. Some evidence highlights the importance of patient acceptability of treatment as some patients refuse particular interventions. An individualized balance between a patient's needs and concerns must be taken into account during selection from a range of nonpharmacologic and pharmacologic antidepressant treatment options.

The use of inconsistent definitions of TRD in the trials and the absence of analyses considering the effect of the number of current treatment failures on outcomes hindered interpretation of data, leading to our use of a tiered system for analyses. The evidence base combining data for Tiers 1–3 on the whole produced findings that were consistent with Tier 1 TRD data and also appear applicable to TRD populations.

Remaining Issues

This area of comparative clinical research is in its infancy. Key areas for future research need primarily to lay more robust foundations for an evidence base that can better inform decisions for clinicians and patients.

The Field Needs a Standard Definition of TRD That Investigators Should use in Their Clinical Trials Research

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by the variability in TRD definitions. Although these definitions appear to be converging on a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it.

Progress in this area of research requires better standardization of this concept, so that future reviews of the evidence do not need to resort to differentiating, as we did, between "Tier 1" studies (i.e., TRD by this definition based on two or more treatment failures) and "Tier 2 or 3" types of studies. The latter do provide information that helps illuminate likely impacts of these interventions on patients with TRD, but that is not the same thing as having robust studies focused clearly on the patient population of greatest interest. The challenge will be to provide a definition that operationalizes TRD to make it feasible for clinicians while at the same time successfully capturing the complexity of treatment resistance.

More Clinical Trials, as Well as Other Possible Study Designs, That Compare Nonpharmacologic Interventions With Other Nonpharmacologic Options and With Pharmacologic Treatments are Necessary to Inform Decisionmaking in TRD

Clinicians, patients, and policymakers need additional relevant data to guide difficult treatment decisions about what to do next: try another medication (and should it be an augmentation, switch, or combination strategy?) or add (or switch to) rTMS, ECT, VNS, or psychotherapy?

Also, given that treatment options for many TRD patients include medications, trials should directly compare nonpharmacologic interventions with each other and with pharmacologic treatments.

The Number of Treatment Failures in the Current Episode Should be Delineated Carefully

This information, more likely to be accurate than lifetime histories of failures, can help investigators determine whether the particular number of failures, or reaching a particular number of failures in a current episode, can help differentiate between nonpharmacologic treatment choices. For example, for patients with two treatment failures in a current episode, the outcomes may not differ between cognitive therapy and rTMS; however, for patients with a different (higher or lower) number of treatment failures in the current episode, one nonpharmacologic treatment may indeed be better than the other. Currently, we do not know what the proper threshold is for selection of treatment. Clarification of the scientific basis for such a decision would substantially improve decisionmaking.

Clarifying Whether Responses Differ for TRD Patients With MDD Compared With Those With Bipolar Disorder Will Help Guide Future Clinical Trial Design

Our decision to include trials with patient populations including up to 20 percent with bipolar disorder (i.e., the "mixed" populations noted earlier) was guided by clinical experience and common sense but not by data. Testing to see whether outcomes differ between the two groups can yield information about inclusion criteria (should the mix be 0 percent, 10 percent, 20 percent, etc.?) that may be useful to investigators in designing TRD trials and may be important to consider as a potential covariate in analyses involving such mixes.

Greater Consideration Should be Given to the Role That the Spectrum of Depressive Severity Plays

Using a finer gradation of depressive severity than investigators now typically employ might identify whether particularly severe degrees of depression, most commonly understood currently as a HAM-$D_{17} \geq 20$, may respond differently to the available nonpharmacologic interventions than do less severe levels of depression. These gradations may lead clinicians to a better understanding of severe depression and its role in guiding treatment selection in TRD.

Direct Comparisons of Treatment Strategies, Holding Consistent any Coexisting or Concomitant Therapies, are Imperative

Decisionmakers need to know whether outcomes with nonpharmacologic treatments are better when such a treatment augments the current treatment, replaces the current treatment, or replaces the current treatment in combination with another treatment. When ongoing treatment is uncontrolled and reflects a variety of treatments—e.g., some patients continue with atypical antipsychotics, some with mood stabilizers, some with no psychotropic medications—results of such studies are difficult, if not impossible, to interpret.

Consistent Reporting of Changes in Depressive Severity, Response Rates, and Remission Rates is Crucial

To allow for better comparisons of clinical outcomes in this difficult-to-treat population, all three measures offer useful information for clinicians. Thus, for either clinical trials or observational studies, investigators should attempt to collect data on all three routinely.

Application of Consistent, Accepted Protocols in Trials is Necessary

Making sure that patients receive equivalent doses of different nonpharmacologic interventions is more difficult than making sure of this for pharmacologic interventions. Nevertheless, investigators designing trials of nonpharmacologic therapies can attempt to do so by implementing standard accepted protocols for their trials. Such "dosing" had been difficult to control when that protocol was in the process of being developed, as with rTMS, but given current treatment parameters, this standardization is a goal well worth trying to reach.

More Careful and Consistent Assessment of Adverse Events is Required

Adverse event reporting is quite limited and tends to cover only a short time span; what reporting does exist is variable and inconsistent. Systematic collection and more consistent reporting of data on harms—that is, adverse events and negative side effects—and information about attrition and withdrawal would provide useful information to help balance information now focused on clinical benefits. Use of the CONSORT statement (available at: http://www.consort-statement.org/home/), which guides proper reporting of study information (including the presentation of adverse events), would strengthen reporting of both harms and other clinical trial findings; it would also aid in the critical appraisal and interpretation of all study results. Further, a more informative assessment of adverse events would require studies to be able to assess long-term and cumulative outcomes.

Including Key Relevant Measures and Subgroups in Subsequent Research is Desirable

As indicated by the review, nearly no evidence exists on how the effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristic (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression; perinatal depression). Also essentially missing is information about health-related outcomes, especially those reported by patients, that concern their quality of life or levels of functional impairment. Subsequent studies should focus on employing known, reliable, and valid measures of patient-reported outcomes, such as the MOS SF-36, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the EQ-5D.

Including Comparisons of Newer Nonpharmacologic Interventions Will be Important in Future Research

As new nonpharmacologic treatments are developed and tested, investigators should try to include them as potential comparators. At the time we started this comparative effectiveness

review, clinical trial data on some of the developing nonpharmacologic interventions, such as magnetic seizure therapy or deep brain stimulation, were insufficient (from the published literature) for us to try to include them. As the evidence bases grow to support the efficacy of such additional nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs.

Conclusion

Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in two cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

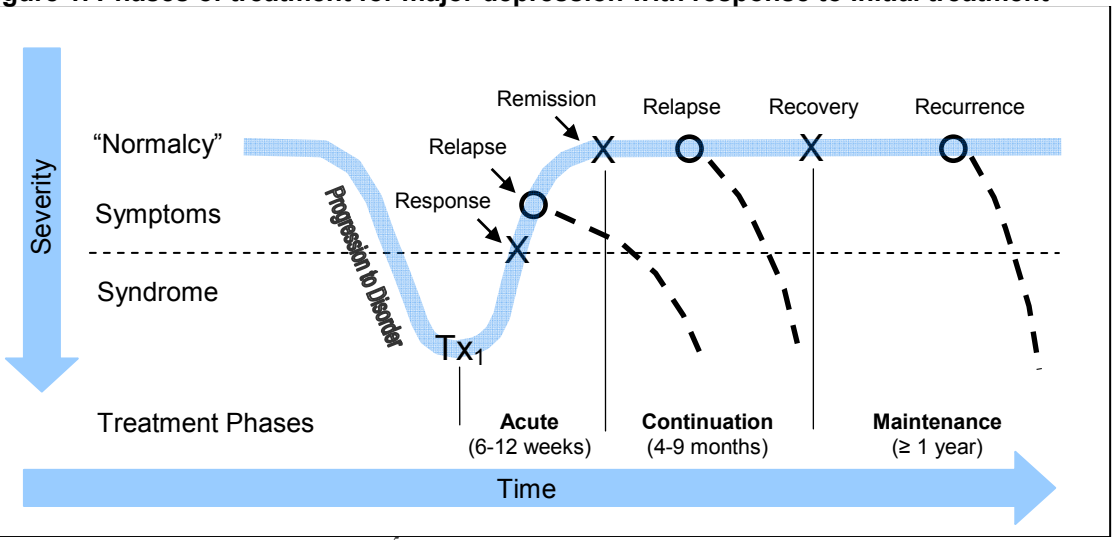
Introduction

Burden and Costs of Disease

Major depressive disorder (MDD) is common and costly. Over the course of a year, between 13.1 million and 14.2 million people will experience MDD.[1] Approximately half of these people seek help for this condition, and only 20 percent of those receive adequate treatment.[2]

Among people who do receive adequate treatment, the normal course of treatment consists of an acute phase lasting 6 to 12 weeks with the goal of remission, meaning a complete resolution of the depressive episode (Figure 1). This is followed by a continuation phase of treatment during which the treatment goal is continued absence of depressive symptoms (i.e., relapse prevention) for an additional 4 to 9 months such that the patient's episode can be considered completely resolved. A maintenance phase lasting an additional 1 or more years is recommended in patients who have had two or more previous episodes of depression to prevent the recurrence of a new depressive episode.[3,4]

Figure 1. Phases of treatment for major depression with response to initial treatment



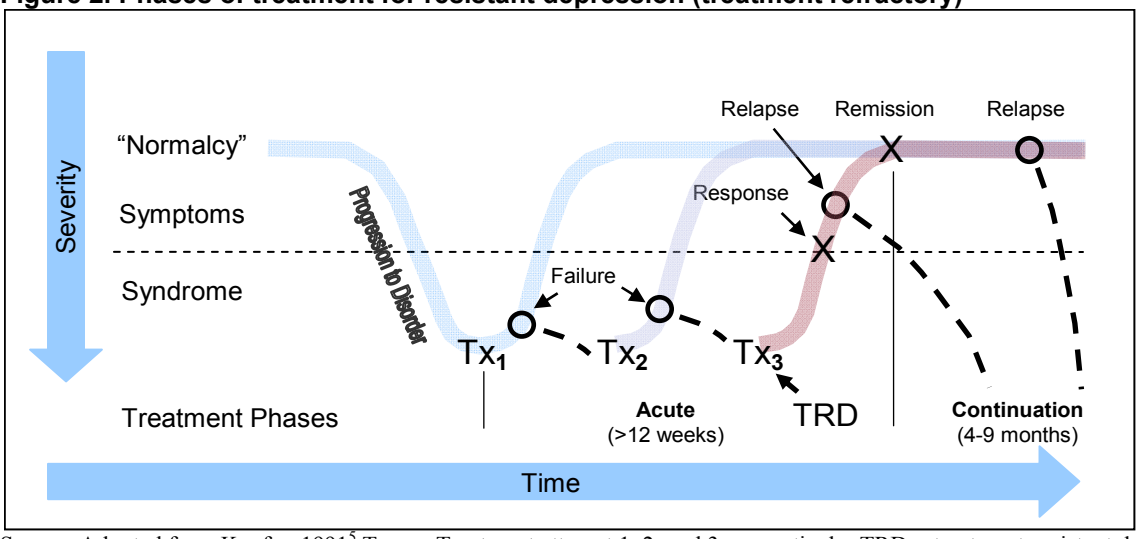
Source: Re-created based on Kupfer, 1991.[5] Tx_1 = treatment attempt 1. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Unfortunately, the course of treating patients with depression (especially MDD) often does not follow the idealized treatment phases of reaching, continuing, and maintaining remission as depicted in Figure 1. In the acute phase of treatment, only 30 percent of patients reach the treatment goal of remission. The remaining 70 percent will either obtain response (usually defined as at least a 50 percent reduction in depressive severity) without remitting (about 20 percent) or not respond at all (50 percent).[6]

This 50 percent of people whose depressive disorder does not adequately respond following acute-phase treatment appear to have a harder-to-treat depression,[7] and this refractory group has generated considerable clinical and research interest.[7] Patients with only one prior treatment failure are sometimes included in this group, but patients with two or more prior failed treatment attempts are a particularly important and poorly understood group[8] and are considered to have

treatment-resistant depression (TRD; see the section below on patient populations included) (Figure 2).[8] Indeed, for patients whose depression does not remit after two adequate treatment attempts in the current episode, the likelihood of recovery with subsequent medication treatment decreases by half to approximately 15 percent.[8] In contrast with Figure 1, which depicts the course of treatment for a patient responding to first-line treatment (i.e., Tx_1), the treatment-resistant patients depicted in Figure 2 require additional treatments (i.e., Tx_2, Tx_3, or more) and thus have prolonged depressive symptoms during unsuccessful acute phase treatment. Patients with two or more treatment failures during the same depressive episode (i.e., those marked as having TRD at Tx_3 in the figure) are also believed to have more resistant disease than patients with two or more prior treatment failures during their entire lifetime. The former group of patients seemingly has a more uncertain prognosis for their condition over time than do patients not seen as treatment-resistant (as defined here); by extension, they face longstanding and greater burden of disease.

Figure 2. Phases of treatment for resistant depression (treatment refractory)



Source: Adopted from Kupfer, 1991[5] Tx_{1-3} = Treatment attempt 1, 2, and 3, respectively; TRD = treatment-resistant depression. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Although TRD broadly is defined as inadequate response following adequate antidepressant therapy in MDD, treatment resistance is a complex phenomenon that is influenced by heterogeneity in depressive subtypes, psychiatric comorbidity, and comorbid medical illnesses.[9] As described in Figure 2, major depression is usually considered treatment resistant when at least two antidepressant attempts have failed.[10] However, criteria for treatment resistance have been variably defined in clinical research and practice. Important factors related to the definition of TRD include the number of failed treatments, the time between treatment attempts, and the adequacy of the dose and duration of antidepressant treatment. The term "pseudo-resistance" has been used to describe patients classified as treatment resistant even though they never actually received an adequate treatment course; pseudo-resistance may account for as many as 60 percent of patients initially classified as TRD.[9]

Patients with TRD incur the highest direct and indirect medical costs among those with MDD. These costs increase with the severity of TRD.[11] Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than six times the mean total

costs of depressed patients who are not treatment resistant.[12] After considering both medical and disability claims from an employer's perspective, one study found that TRD employees cost $14,490 per employee per year, whereas the cost for non-TRD employees was $6,665 per employee per year (1996–1998).[13]

Purpose of This Report

Given the burden of TRD generally, the uncertain prognosis of the disorder, and the high costs of therapy, clinicians and patients need clear evidence to guide their treatment decisions. The choices are wide ranging, include both pharmacologic and nonpharmacologic interventions, and are fraught with incomplete, potentially even conflicting, evidence. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for patients with TRD. Antidepressant medications, which are the most commonly used intervention, have decreasing efficacy for producing remission after patients have experienced two failures. Such drugs also often have side effects,[8] sometimes minor but sometimes quite serious.[14] For these reasons, clinicians often look for alternative strategies for their TRD patients.

This comparative effectiveness review (CER) is intended to help various decisionmakers come to informed choices about the use of nonpharmacologic interventions for TRD in adults. Our principal goal is to summarize comparative data on the efficacy, effectiveness, and harms of electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT) in patients with TRD. Comparisons between two or more nonpharmacologic interventions are our main interest; however, because patients with TRD and their clinicians often decide between another medication treatment and a nonpharmacologic option, we also compare nonpharmacologic options with pharmacologic ones, both directly and indirectly. The goal is to produce a rough estimate of how these strategies compare for this patient population.

Included Interventions

Nonpharmacologic somatic treatments and nonsomatic psychotherapy treatments offer alternatives to antidepressant medications, although the evidence base for many of these treatments is limited. At the time the protocol for this review was developed, only four types of interventions had an evidence base sufficient to establish their efficacy and therefore be considered appropriate for a CER. Interventions that offer promising options for patients with TRD include ECT, rTMS, VNS, and evidence-based psychotherapy (e.g., cognitive therapy, such as cognitive behavioral therapy [CBT or IPT]). In some cases, these therapies or procedures can be used in combination (e.g., ECT and rTMS). Table 1 provides a summary of these principal nonpharmacologic interventions, including their uses, technical parameters, common side effects, and contraindications. They are described in more detail below. Generally, although these interventions may be safe and effective options for TRD, little evidence exists to guide decisions about their comparative efficacy. Further, how the nonpharmacologic options compare with pharmacologic treatments remains unclear.

Electroconvulsive Therapy (ECT)

ECT has been available for use in the United States since the 1930s. Current evidence indicates that ECT has a role in the treatment of people with depression and in certain subgroups

of people with schizophrenia, catatonia, and mania.[15,16] Its primary current role in depression is for treatment resistance or intolerance.[17] Because ECT was introduced prior to U.S. Food and Drug Administration (FDA) device regulation, it was not subjected to formal review and approval as a device. It has since been classified as a class III device, which means that

Table 1. Summary of nonpharmacologic interventions covered in this report

Major Factors About Nonpharma-cologic Interventions	Electroconvulsive Therapy (ECT)	Repetitive Transcranial Magnetic Stimulation (rTMS)	Vagus Nerve Stimulation (VNS)	Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT)
Description	Passing an electric current through the brain after administering anesthetic and muscle relaxants, to produce a convulsion	Focal magnetic stimulation through the scalp without the use of anesthesia[18]	Surgically placed electrodes around the left vagus nerve to modulate mood and control seizures	Psychotherapy to identify negative depressogenic cognitions[19] or interpersonal behaviors[20]
Uses	Depression, schizophrenia, catatonia, mania	Depression, mania, anxiety, schizophrenia, epilepsy, Parkinson's disease[21]	Depression, epilepsy	Depression, bipolar disorder, psychosis, anxiety, personality disorders, eating disorders
Common Placement Sites	Bifrontal/bilateral or unilateral electrode placement	Dorsolateral prefrontal cortex	Left vagus nerve	Not applicable
Average Duration	Administered 2 or 3 times a week for 3-4 weeks[22]	40 minutes daily (usually weekdays) for 2-6 weeks[23]	30 seconds every 5 minutes, generally for 10 weeks[24]	Weekly sessions for 3-4 months
Usual Dosage	Millicoulombs of charge[17]	<1-20 Hertz	Current >1 milliamperes (mA), Frequency 1-145 hertz	Not applicable
Contra-indications	Increased risk of complications in patients with unstable cardiac disease, ischemia, arrhythmias, hemorrhage, or increased intracranial pressure[17]	Presence of conductive, ferromagnetic, or other magnetic-sensitive metals in the head or within 30cm of the treatment coil. Presence of implants controlled by physiological signals.[25] Patients with high risk of seizure.	Bilateral or left cervical vagatomy. Patients with implants should not receive short wave diathermy, microwave diathermy, or ultrasound diathermy.	Patients with cognitive disorders, cognitive impairment, or limited cognitive functioning

"insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness." (21 CFR860.3) The FDA is reconsidering how it classifies ECT.[26]

ECT involves passing an electric current through the brain to produce a convulsion. Electrodes are usually placed at the bifrontal, bilateral, or right unilateral position. It is not commonly used as a first-line therapy or in primary care practice. The exceptions are uses in an emergency in which the person's life is at risk because of refusing to eat or drink or being in a catatonic state or in cases of attempted suicide. The effectiveness of ECT may be related to the stimulus parameters used, including position of electrodes, dosage, and waveform of electricity.

ECT is covered by major insurance plans, Medicaid, and Medicare. Reimbursement is approximately $275 per treatment,[27] independent of the costs of inpatient hospitalization, should it be required. ECT usually consists of two to three treatments per week for 3 to 4 weeks.

ECT shows greater improvement in patients with suicidal intent than other antidepressant treatments; thus, it may be used as an early therapeutic option in suicidal patients.[28] Research also indicates that despite physical illness, coexisting diseases, or cognitive impairment, older patients tolerate ECT as well as younger patients and may demonstrate better response.[29,30] Because ECT is a procedure that involves anesthesia, it also poses slight risks to patients from the procedure itself. Other potential risks include seizure and adverse cognitive effects.[17]

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS involves magnetic focal stimulation through the scalp. The current elicited by the electromagnetic coil stimulates nerve cells in the region of the brain involved in mood regulation and depression. It can be administered in an office setting without the use of anesthesia. Patients may perceive it as less threatening than ECT.[31] Patients having conductive, ferromagnetic, or other magnetic-sensitive metals in the head or within 30cm of the treatment coil should not undergo this procedure.[25] Sessions are usually 40 minutes in length, administered daily (usually only weekdays) for 2 to 6 weeks. rTMS costs between $100 and $300 per session.[31,32] Medicare does not cover rTMS, although some private insurance plans cover it under limited circumstances.

rTMS is usually considered a reasonable option for acute treatment of TRD as opposed to VNS and pharmacotherapy, which are predominantly used as long-term treatments for TRD.[33] The FDA first approved this device in October 2008. The FDA states that rTMS is "indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode."[34] Possible side effects with rTMS include mild headaches, syncope, and transient hearing changes.[23] Although rTMS does pose a risk of seizure,[35] it reportedly does not have the cognitive risks of ECT.[23]

Vagus Nerve Stimulation (VNS)

VNS involves surgically placed electrodes around the left vagus nerve. The VNS device consists of a round battery-powered generator that is implanted into the chest wall and attached to wires threaded along the vagus nerve. The therapy includes minor surgery, lasting approximately 30 to 60 minutes. Once implanted, the generator pulses the nerve for 30 seconds once every 5 minutes.[36] The total duration of this intervention is generally 10 weeks, although the stimulation can be extended for longer intervals.[24]

VNS was first used in patients with epilepsy; it was also found simultaneously to improve mood.[37] The FDA approved VNS for TRD in July 2005, with labeled indication for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments."[38] The Centers for Medicare and Medicaid Services decided not to cover VNS in February 2007, citing lack of evidence.[36] VNS devices cost approximately $10,000 to $20,000, not including the cost of surgery and hospital fees. Although the initial cost of VNS is very high, it may save money for TRD patients in the long run. One study reported long-term savings with VNS compared with usual TRD care, estimating savings of $2,974 and $23,539 per patient per year at 5 and 8 years of device life, respectively.[39]

The place in therapy for VNS may be for patients who have four or more adequate antidepressant treatment failures.[40] Considerations also include a longer onset of antidepressant action than other treatments, as VNS benefits for TRD may not be fully realized for 6 to 12 months.[41] Further, VNS poses surgical risks and is associated with several side effects such as voice alteration, cough, neck pain, paresthesia, and dyspnea.[42]

Cognitive Behavioral Therapy (CBT) or Interpersonal Psychotherapy (IPT)

Use of CBT began in the 1960s. It is a type of psychotherapy that aims to modify distorted, maladaptive, and depressogenic cognitions and related behavioral dysfunction.[19] The therapist first introduces the patient to the cognitive model. Agendas, feedback, and psychoeducational procedures are used to structure sessions. To treat depressed patients with CBT, therapists emphasize negatively distorted thinking and deficits in learning and memory functioning.

Developed in the 1970s, IPT helps patients explore social and interpersonal issues that relate to depressive symptoms. Depressive symptoms identified are related to one of the four key problem areas: grief, disputes, transitions, and deficits.[20] After selecting a focus area, later sessions help the patient develop strategies to deal with the problem.[43]

Both CBT and IPT have been studied extensively for depression, eating disorders, anxiety, and personality disorders, but understanding of their role in the treatment of TRD is more limited. Both therapies involve weekly sessions with the therapist, which last for 30 to 60 minutes. CBT may be carried out in a group setting if deemed beneficial for the patient. The therapy generally lasts from 3 to 4 months for acute phase treatment, although treatment duration may be for longer periods. Costs of CBT and IPT depend on the facility and the therapist; on average, these interventions cost around $150 per session. Medicare currently covers CBT and IPT. FDA approval is not required for CBT or IPT since they do not include drugs or devices.

CBT and IPT do not have any risks or side effects associated with them. Patients need to have normal cognitive functioning to comprehend the therapist's questions. CBT and IPT are comparable psychotherapies for major depression and appear to be as effective as antidepressant medication treatment,[44-46] although CBT may be more effective in patients with severe depression.[43]

Pharmacologic Interventions

For many patients with TRD, the consideration of another pharmacologic intervention (whether a single agent or combination) remains the next decision step. To place the comparative effectiveness of nonpharmacologic treatments within the context of pharmacologic considerations, we also consider clinical outcomes for a next step pharmacologic treatment based on augmentation and combination medications commonly used in clinical practice.[47] Given the limited evidence base addressing this topic for TRD, we only consider pharmacologic information for clinical outcomes during acute phase treatment for our main population of interest (see Key Question [KQ] 1b below).

Patient Populations Included

Treatment resistance defined by prior treatment failures. The primary focus of this review is on patients with MDD who have had two or more failed prior treatment attempts within the current episode. Definitions of TRD vary considerably and controversially, most often by the

number of treatment failures (e.g., one failure, or one or more failures, or two or more failures), whether the treatment failures occur during the current episode, and whether treatment failures required different classes of antidepressants; no universally accepted definition of TRD currently exists.[7,48-51] This variability is reflected in the differing operational definitions and selection criteria used for TRD trials. Nevertheless, a consensus appears to be forming around a definition of two or more treatment failures in the current episode.[9,48] We view the most applicable evidence to be derived from *patients with two or more failures of treatment attempts that are of adequate dose and duration during the current depressive episode*. This population represents a group with known treatment resistance, and we believe these studies are most relevant to our KQs concerning efficacy, effectiveness, safety, and tolerability. However, given the evolving nature of the TRD definition, studies have often not clarified the number of failures within the current episode. Consequently, for the purposes of this report, we will define TRD as ***an episode of MDD that has not recovered following two or more adequate antidepressant medication treatments, regardless of the class of antidepressant used or whether the treatment failures were required to be in the current episode***.

The variance of the TRD classification makes interpretation of the available data involving our interventions of interest challenging. Studies addressing TRD and these nonpharmacologic interventions are not always designed with the above specifications in mind. Rather, some studies focus more broadly on the efficacy and/or safety of the interventions in populations of patients with poorly specified characteristics with respect to treatment failures. In particular, they may require patients to have only one previous treatment failure rather than two, or they may be conducted in samples of patients for whom the investigators have not been completely clear about failures but still give enough information to regard the subjects as "probable" failures (e.g., patients referred for ECT). In such studies, baseline characteristics may provide data indicating that a subset of these patients have two or more treatment failures; however, it is often unclear what proportion of the sample would fit the TRD definition of two or more failures selected for this report. Although these study populations do not involve homogenous TRD populations, their samples likely include a substantial proportion of TRD patients, and hence can provide data relevant to TRD. Consequently, although we will focus on studies strictly meeting our TRD definition, we will secondarily consider how data from two other groups of studies—those requiring one or more treatment failures (which involve patients with only one treatment failure as well as those with TRD) and those with probable TRD—may enhance our results.

Treatment-resistant depression defined for two classes of mood disorder. Studies of treatment resistance often consider patients with bipolar disorder in addition to patients with MDD. Our primary focus is evidence about TRD in study patients who clearly have MDD and not any another mood disorder. However, clinical trials of TRD patients frequently allow a mixture of MDD and bipolar disorder in their samples. Given that depressive episodes in MDD may have a different prognosis than those in bipolar disorder,[52] such a mixture may distort the true effect seen in MDD-only patients. At the same time, studies in which a small fraction of the patient population has bipolar disorder rather than purely MDD are still likely to produce some information on the main topic (i.e., MDD alone). We attempted to select a threshold that would allow inclusion of studies with a proportion of bipolar disease that would not change the likelihood of response. No evidence exists that indicates a proper threshold for such a mixture. After conferring with a Technical Expert Panel, we chose to include trials in our synthesis when the patient population as a whole consists of no more than 20 percent bipolar patients, assuming that such a mix would not substantially alter outcomes from what one would see with MDD

alone. The type of bipolar diagnosis could include Type 1 (with manic episodes) or Type 2 (with hypomanic episodes).

Scope and Key Questions (KQs)

This review compares the efficacy, effectiveness, and harms of nonpharmacologic interventions for TRD in adults. To that end, we address the following six KQs. "Trials" in these KQs refers to treatment attempts, not experimental studies.

- KQ 1a. For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic[1] intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- KQ 1b. How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?
- KQ 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?
- KQ 3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?
- KQ 4. For adults with TRD, do nonpharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.
- KQ 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations:
    - Elderly or very elderly patients; other demographic groups (defined by age, ethnic or racial groups, and sex)?
    - Patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer)?
- KQ 6. For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Organization of the Report

The remainder of this report describes our methods, presents the results of our synthesis of the literature, discusses our conclusions, and provides other information relevant to the interpretation of this work. The Methods chapter describes our scientific approach for this comparative effectiveness review in detail. The Results chapter presents our findings for all the KQs and subquestions; it includes summary tables as well. In the Discussion chapter, we summarize the findings, present the strength of evidence for critical comparisons or outcomes, and discuss the implications for practice and further research. A complete list of references is located immediately following the discussion chapter.

This report also contains the following appendices. Appendix A contains the exact search strings we used in our literature searches. Appendix B documents all the data abstraction forms and our quality rating criteria. Our excluded studies with reasons for exclusion are presented in Appendix C. Evidence tables appear in Appendix D. Appendix E is our table of scales used for measuring neurocognitive and other adverse effects. Appendix F lists our poor-quality studies and reasons for exclusion from relevant KQ analyses. Appendix G lists all sources from which we identified all of the studies for this review. Finally, Appendix H provides a listing of studies recommended for inclusion by peer and public reviewers of the prior draft version of the report. It is added here to help current readers of this report understand why well-known studies did not meet the inclusion criteria for this comparative effectiveness review.

Methods

In this chapter, we document the procedures that the Evidence-based Practice Center (EPC) used to develop this comparative effectiveness review (CER) on nonpharmacologic treatments for adults with treatment-resistant depression (TRD). We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

The topic of this CER and preliminary questions arose through an open process involving the public, the Scientific Resource Center (SRC) for the Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) at Oregon Health and Science University, and various stakeholder groups. Our EPC was asked to develop provisional Key Questions (KQs) based on the issues submitted by the nominator of the topic. We conducted a preliminary literature review and worked with key informants to develop a set of provisional KQs. These KQs were posted by AHRQ for public comment before they were assigned to the RTI International-University of North Carolina EPC for this full CER.

Technical Expert Panel

In designing the study questions and methodology at the topic development stage, we consulted several technical and content experts, seeking broad expertise and perspectives. We worked with seven key informants and all were invited to participate in the Technical Expert Panel (TEP) for the full CER. Five accepted, and in one case a replacement from the consumer organization was made because the original person was no longer with the organization. In addition, we invited an expert in psychotherapy and another psychiatrist conducting a similar evidence review on pharmacotherapy options after one failed treatment, creating a total of eight members (listed in the Acknowledgements). We note that two TEP members had undisclosed conflicts of interest (COIs) related to the repetitive transcranial magnetic stimulation (rTMS) device that were identified during the course of the project. Upon further inquiry and clarification of the specifics of the form, both individuals filed amended COI forms.

To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. Specifically, TEP members participated in conference calls and discussions through e-mail to:

- Review the KQs and analytic framework at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria and the review of the protocol; and
- Provide input on the information and categories included in evidence tables.

Our KQs were posted on AHRQ's Effective Health Care Web site on December 9, 2009. After discussions with the TEP, we added an additional question, KQ 1b, as described in the Introduction chapter.

Literature Search

Databases and Search Terms

To identify articles relevant to each of the six KQs defined in the Introduction chapter, we searched MEDLINE, Embase, the Cochrane Library, PsycINFO, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix A. We used Medical Subject Headings (MeSH or MH) as search terms when available as well as key words when appropriate. The first step was to locate all articles on depression in human adults published in English. We combined terms for treatment-resistant depression, including the terms refractory, resistant, and drug resistance. The search was further narrowed to specific pharmacological and nonpharmacological treatments. Nonpharmacological interventions included socioenvironmental therapy, interpersonal psychotherapy (IPT), psychotherapy, cognitive therapy, cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS). We searched for systematic reviews, clinical controlled trials, and nonexperimental studies in which the investigator did not assign group allocation. Sources were searched from 1980 to November 18, 2010.

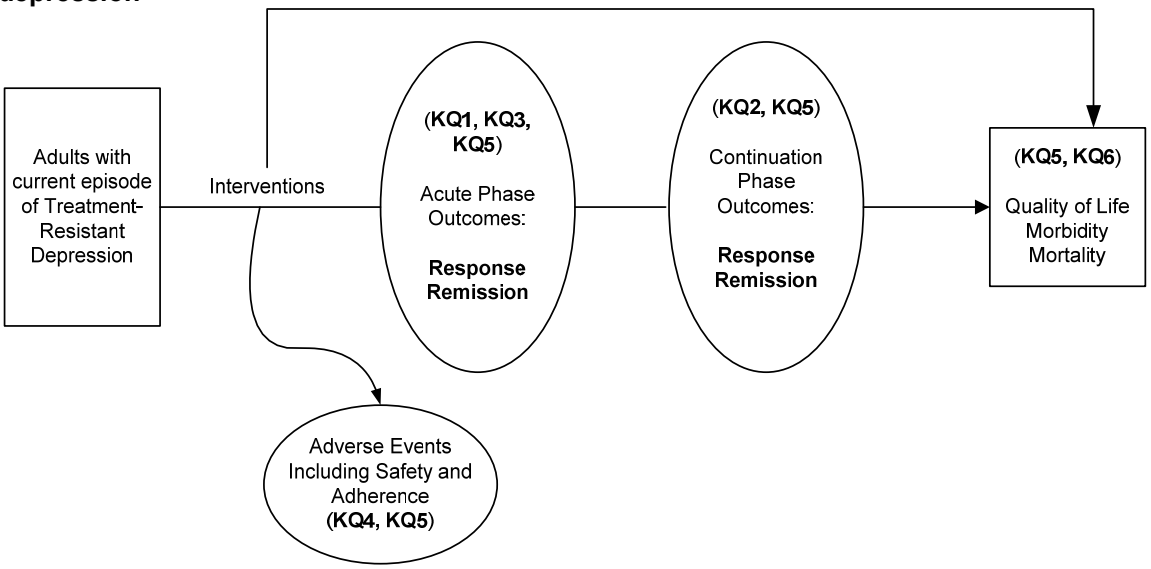
We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We also manually searched reference lists of pertinent review articles and letters to the editor. We imported all citations into an electronic database (EndNote X3). Additionally, we hand-searched the Center for Drug Evaluation and Research database to identify unpublished research submitted to the U.S. Food and Drug Administration.

AHRQ SRC staff contacted device manufacturers and invited them to submit dossiers, including citations. We reviewed dossiers received from Cyberonics and Neuronetics. The SRC also provided our EPC with the results of their gray literature search: relevant articles, conference proceedings, and meeting abstracts to assist our center to identify other eligible studies that may not have been captured in the literature search.

Analytic Framework

Based on the six KQs, we developed an analytic framework to guide the systematic review (Figure 3). Specifically, the first two KQs pertain to the efficacy and effectiveness of obtaining (KQ 1) and maintaining (KQ 2) response and remission using these nonpharmacologic treatments; KQ 1 addresses the acute phase of treatment and KQ 2 the continuation or maintenance phases of treatment (as depicted in Figure 3). KQ 3 addresses response and remission for psychiatric subtypes of TRD (e.g., coexisting anxiety) and KQ 5 focuses on certain population subgroups (e.g., the elderly). KQ 4 focuses on safety and tolerability issues—that is, harms—with each of the interventions. Finally, KQ 6 looks at how these interventions affect other health outcomes, such as quality of life.

Figure 3. Analytic framework for nonpharmacologic interventions for treatment-resistant depression



Study Selection

To summarize, interventions included for one or more of the key questions (KQs) are:

- Nonpharmacologic therapies, for KQs 1–6:
  - ECT
  - rTMS
  - VNS
  - Evidence-based psychotherapy, specifically cognitive therapy (CBT or IPT)
- Pharmacologic,[47] for KQ 1b only, at least one of the antidepressants listed below:
  - Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
  - Serotonin-norepinephrine reuptake inhibitors: desvenlafaxine, duloxetine, mirtazapine, venlafaxine
  - Serotonin modulators: nefazodone and trazodone
  - Tetracyclic: mirtazapine
  - Other antidepressants: bupropion
  - Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, mianserin, nortriptyline
  - Monoamine oxidase inhibitors (MAOIs): phenelzine, tranylcypromine
  - Augmentation strategies with methylphenidate; T4/cytomel; liothyronine; buspirone; lithium or amilsupride; apripazole; olanzapine; quetiapine; risperidone; ziprasidone.

For each KQ, we specified inclusion and exclusion criteria for studies and specified the outcome measures of interest (Table 2). For efficacy and effectiveness (all KQs except KQ 4), we first focused on head-to-head RCTs comparing one intervention with another. This body of work provides direct evidence about the comparisons. When sufficient head-to-head evidence was unavailable, we evaluated placebo- or sham-controlled evidence; in some cases, studies might have used "treatment as usual" as the control arm. In any of these cases, the evidence provides only indirect evidence. Systematic evidence reviews or meta-analyses based on a

systematic literature search were eligible for inclusion for each KQ. For reviewing adverse events (KQ 4), per our standard approach, we include observational studies. Finally, given the dearth of randomized controlled data that our preliminary review suggested was available for KQ 3 on psychiatric subtypes, KQ 5 on subgroups, and KQ 6 on quality of life, for these KQs we included observational studies (limited to prospective and retrospective cohort studies and case control studies). We do not formally distinguish efficacy from effectiveness trials.

Table 2. Key questions, outcomes, and study eligibility by key question

Key Question and Outcomes	Study Eligibility Criteria (Inclusion and Exclusion Criteria)
KQ 1a and 1b **Efficacy and effectiveness** Outcomes • Response • Remission Measurement Scales • Hamilton Rating Scale for Depression Scale (HAM-D) • Montgomery-Åsberg Depression Rating Scale (MADRS) • Beck Depression Inventory (BDI) • Inventory of Depressive Symptomatology • Clinical Global Impression (CGI) • Other relevant scales if none of the above is reported (e.g., Patient Health Questionnaire [PHQ-9])	**Study design** KQ 1a: • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. pharmacologic (an antidepressant, with or without additional pharmacologic agent[s]) • Good- or fair-quality meta-analyses or systematic evidence reviews KQ 1b: • RCTs of nonpharmacologic vs. placebo or sham • RCTs of pharmacologic (an antidepressant, with or without additional pharmacologic agent[s]) vs. placebo or sham • Good- or fair-quality meta-analyses **Minimum study duration** • Any duration **Sample size** • No minimum
KQ 2 **Maintenance of response or remission (or prevention of relapse or recurrence)** Outcomes • Relapse (continuation phase) • Recurrence (maintenance phase) Measurement Scales • All efficacy/effectiveness scales (see KQ 1 above)	**Study design** • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • RCT designs include continued treatment for prevention or assessment of duration of effect after treatment stopped • Good- or fair-quality meta-analyses or systematic evidence reviews **Minimum study duration** • ≥ 1 month for relapse prevention • ≥ 3 months for recurrence prevention **Sample size** • No minimum
KQ 3 **Efficacy and effectiveness by subtype** Outcomes • Response • Remission Measurement Scales • All efficacy/effectiveness scales (see KQ 1 above) Symptom Subtypes • Psychotic-paranoia/hallucinations • Melancholic • Atypical • Postpartum	**Study design** • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses or systematic evidence reviews • Observational studies (limited to prospective and retrospective cohort studies, case control studies) **Minimum study duration** • Any duration **Sample size** • No minimum

Table 2. Key questions, outcomes, and study eligibility by key question (continued)

Key Question and Outcomes	Study Eligibility Criteria (Inclusion and Exclusion Criteria)
KQ 4 **Safety, adverse events, and adherence** Outcomes • Neurocognitive ◦ Amnesia ◦ Memory loss • Headaches • Postoperative complications • Other reported events • Discontinuations • Adherence/compliance Measurement Scales • All reported adverse events measurement scales • Discontinuations (overall and attributed to adverse events) • Adherence or compliance measures	**Study design** • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) **Minimum study duration** • Any duration **Sample size** • No minimum, case reports excluded
KQ 5 **Population subgroups** Outcomes • Response/remission • Relapse/recurrence • Adverse events • Discontinuations Measurement Scales • All efficacy/effectiveness scales (see KQ 1 above) • All reported adverse events measurement scales (see KQ 4 above) • Discontinuations and adherence rates Population Subgroups • Age • Medical comorbidity • Race or ethnicity	**Study design** • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) **Minimum study duration** • Any duration **Sample size** • No minimum, case reports excluded
KQ 6 **Health-related outcomes** Outcomes • Quality of life • Satisfaction/enjoyment • Physical or mental functioning • Work productivity or employment Measurement Scales • Global Assessment of Functioning Ability (GAF) • Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) • Medical Outcomes Study Short Form (SF-36, SF-12 or others) • Employment/productivity scales • Activities of daily living • Other relevant measures	**Study design** • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) **Minimum study duration** • Any duration **Sample size** • No minimum

KQ = key question; RCT = randomized controlled trial

Two people independently reviewed article abstracts using the criteria presented in Appendix B for Level One. If both reviewers agreed that the study did not meet eligibility criteria, we excluded it; otherwise it moved forward to the next step for full-text review, Level Two. We retrieved the full articles for all studies retained at this stage.

Two reviewers then independently reviewed the full-text articles and applied a more detailed set of inclusion criteria; these involved explicit reasons for exclusion, such as wrong intervention, and wrong or no comparison group. Appendix B includes copies of all reviewer forms. We resolved conflicts about inclusion at this stage through consensus, with conflicts adjudicated by a third party. Studies excluded at this stage, along with reasons for exclusion, are listed in Appendix C.

For this review, results from well-conducted, valid head-to-head trials—that is, direct comparisons—provide the strongest evidence to compare treatments with respect to efficacy and harms. The many possible comparisons, set out in the Introduction chapter, are complex; in some cases, studies compared a treatment with a combination of that treatment and a second intervention. We defined head-to-head trials as those comparing one treatment with another treatment either by itself or in combination with other interventions.

We did not examine placebo-controlled or sham-controlled trials in detail if a sufficient number of head-to-head trials were available. If the published head-to-head evidence was limited, we reviewed placebo-controlled trials to provide an overview of efficacy. For harms (i.e., evidence pertaining to tolerability and adverse events), we examined data from both experimental and observational studies.

We did not set any minimum criteria for study duration or sample size, though case reports were excluded when observational study designs were allowed. The exception to this involved relapse and recurrence prevention studies, for which we required at least 1 and 3 months of followup, respectively.

We reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness, for example, were a decrease in depressive severity, treatment response and remission, quality of life, relapse, functional capacity, and hospitalization. We reviewed response and remission when based on changes in scores on depression scales as proxies for health outcomes (e.g., 50 percent improvement of depression scores for response). For harms, we looked for both overall and specific outcomes related to neurocognitive functioning, specific adverse events (e.g., amnesia, memory loss, headache), and procedure-related complications, recorded systematically and spontaneously, as well as tolerability as reflected by withdrawals and withdrawals attributable to adverse events.

Data Extraction and Analytic Strategy

We designed and used a structured data abstraction form to ensure consistency of data abstraction and quality appraisal for each study (reproduced in Appendix B). All data abstraction originally employed SRS 4.0 Mobius Analytics (available at: www.mobiusanalytics.com/e/index.cfm). Trained reviewers abstracted data from each included study into predesigned evidence tables for each KQ; they also assigned an initial quality rating (described below). A senior reviewer read each abstracted article, evaluated the accuracy and completeness of the data abstraction, and independently did a second quality rating. Final evidence tables can be found in Appendix D.

We abstracted data on study design, baseline population characteristics, specifications of the intervention, and relevant outcome assessments for both efficacy and harms. We abstracted data for the efficacy and quality-of-life outcome assessments when the studies used validated measures. We also abstracted data on compliance, attrition, and harms. Finally, we recorded whether analyses were done according to intention-to-treat methods if such information was

available in the articles. A detailed list of the data elements abstracted is presented in Appendix B.

Treatment Resistant Depression Definition and Tier Classification

As already noted, the definitions of TRD vary along several dimensions: How many previous treatment failures are considered? What types of treatments failed? Were dose and duration of previous treatments adequate? Were the failures during the current episode or over a lifetime? Moreover, the populations included in clinical studies differ by numerous factors. In regard to the variability of the definitions used in studies of TRD, as laid out in the Introduction chapter, we extracted specific information to create the three-tiered classification system used in presenting results in the Results chapter. We specifically collected data on the study's definition of a failed "trial" (i.e., a treatment in this context). These variables included a specific drug or drug class failed, the specified duration and/or dose of an "adequate" trial, the number of failed trials (whether in the current episode or in a previous, "lifetime," episode) required for inclusion, and baseline characteristics (i.e., the mean number of failed trials and other pertinent descriptors) of the sample.

Although our working definition of TRD is two or more treatment failures, we realize that many studies involving TRD populations often do not use this definition when formulating their inclusion criteria and that these criteria may not accurately reflect the average number of failed antidepressant trials for a study population. For example, although some studies may require only a single antidepressant failure for a participant to be included in a study, the inclusion criteria may not accurately indicate the average number of antidepressant failures for the study population, which could be higher than the cut point set by study inclusion criteria.

When devising the analytic strategy for this report, variation in study inclusion criteria and the overlap in the actual number of antidepressant failures were considered. As a function of our preliminary literature review, we realized that evolving definitions of TRD might prevent inclusion of studies with data relevant to our population of interest. For example, studies conducted at a time when resistance was understood to be one or more treatment failures might have nearly a complete population of patients with TRD (two or more treatment failures), but because the analyses did not allow results to be stratified by having two or more treatment failures, such a study would be excluded. Also, studies in which the number of prior treatment failures was not specified but where the likelihood of TRD was high, such as with many ECT trials, would also be excluded. We believed that not including such studies would not accurately reflect the available evidence base for TRD.

Accordingly, we considered options and discussed possible approaches with our TEP, who supported the use of a tiered study classification system. We have attempted to maintain our focus on study populations meeting our TRD definition ($\geq$ 2 antidepressant failures) while not excluding potentially relevant evidence.

Our approach to stratifying the literature—into three "tiers"—is highlighted in Table 3. We primarily differentiate studies based on how investigators for the included studies defined TRD:

Table 3. Relevance to TRD per CER protocol by Tiers of evidence pertaining to populations involving varying proportions of treatment-resistant depression

Population	Tier 1. TRD per CER Protocol (All Patients Required to Have ≥ 2 Treatment Failures)	Tier 2. All Patients Required to Have ≥ 1 Prior Treatment Failures	Tier 3. Involves Those With Probable TRD (But Number of Treatment Failures not Specified)
MDD alone	All MDD patients who failed ≥ 2 previous treatments	All MDD patients who failed ≥ 1 previous treatment	All MDD patients with TRD not defined
Mixed MDD and bipolar disease, with bipolar patients constituting > 0% but ≤ 20% of the study population	MDD/bipolar mix who failed ≥ 2 previous treatments	MDD/bipolar mix who failed ≥ 1 previous treatment	MDD/bipolar mix with TRD not defined

CER = comparative effectiveness review; MDD = major depressive disorder; TRD = treatment-resistant depression

- **Tier 1** evidence: involves studies requiring failure to recover following two or more adequate antidepressant treatment trials (Tier 1, our working definition of TRD).
- **Tier 2** evidence: involves studies requiring patients to have one or more failed adequate antidepressant treatment trials; may include both those with only one prior treatment failure in addition to those with two or more failed trials. By virtue of including those with only one failure, on average this group has an overall lesser degree of treatment resistance than TRD patients (Tier 1).
- **Tier 3** evidence: involves studies where the number of prior failed treatments was not specified but the clinical situation suggested a high probability of patients having two or more failed prior antidepressant trials; these data have probable relevance to TRD. For example, an included study may refer to TRD without characterizing it, or the clinical presentation may strongly suggest two or more prior treatment failures. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

Psychiatric Diagnosis

Also, as described in the Introduction chapter, we included study populations of patients with major depressive disorder (MDD) and study populations that include a small number of patients with bipolar disorder. We explicitly extracted data regarding the psychiatric diagnosis—that is, MDD or bipolar disorder—to allow us to limit the percentage of patients with a bipolar TRD to ≤ 20 percent, a proportion that we determined would be unlikely to influence the outcomes from what was expected for an MDD TRD population. If the study clarified whether the included bipolar patients were Type 1 (with manic episodes) or Type 2 (with hypomanic episodes), we collected this information.

Nonpharmacologic Intervention Treatment Characteristics

During data abstraction, characteristics of each mode of nonpharmalogical intervention that affected treatment dose or intensity were collected and used in our analytic approach. Parameter variables were unique for each mode of intervention. For ECT, data were collected on the location of the stimuli (e.g., unilateral/bilateral), treatment intensity (e.g., as a function of seizure threshold), number of treatments per week, and mean number of treatment sessions. In the

Results chapter, ECT implementation for an intervention group is described using the proportion receiving bilateral stimulation and the mean number of treatment sessions received; additional treatment description parameters are listed in the evidence tables (Appendix D).

For rTMS, data were abstracted on the location of stimuli (e.g., left or right dorsolateral prefrontal cortex); frequency (e.g., hertz [Hz]) and intensity (e.g., as a function of motor threshold) of the stimuli; stimuli or pulses per session (abbreviated "pps"); total number of sessions; and duration of treatment (in weeks). These variables were not always presented in this fashion within our included studies. The following formula was used to calculate pps when the number of treatments per week was not explicitly provided: frequency (Hz) times the duration of each train (seconds) times the number of trains equals pps.[21]

A range of treatment parameters for both active and sham stimulations are used in rTMS efficacy studies. In the treatment of depression, stimuli are most often applied at either a high frequency (> 1 Hz) to the left or low frequency (≤ 1 Hz) to the right dorsolateral prefrontal cortex.[21] To simplify reporting in the Results chapter, the location of stimulation and frequency is specified only in studies deviating from these conventions. All other interventions are described as either high rTMS or low rTMS and complete descriptions of all rTMS stimulation parameters as provided in individual studies are reported in the evidence tables (Appendix D).

Some methods of sham rTMS have been shown to have a smaller but noteworthy amount of active stimulation.[53,54] If an included study used one of these methods of sham stimulation, investigators assessed the possibility that it affected the results of the study with potential issues acknowledged in the description of the results. Full descriptions of all sham stimulation parameters are found in the evidence tables (Appendix D).

For VNS, data were collected on the frequency (Hz), pulse width (in seconds), on/off cycle schedule, and duration of treatment. Only treatment parameters outside of the standard range are described in the results; full intervention methodologies, including sham stimulation procedures, are presented in the evidence tables (Appendix D).

Lastly, for psychotherapeutic interventions, data were collected on the method of therapy implementation (i.e., individual or group therapy), content of the curriculum (e.g., cognitive-based therapy), intensity of the treatment (in sessions per week), total number of sessions, and treatment duration (in weeks). Psychotherapeutic interventions are defined by curriculum content in the results; other parameters are reported in the evidence tables (Appendix D).

Antidepressant Medication Treatment Strategy

In addition to the nonpharmacologic interventions used in studies, investigators used different strategies for managing patients' antidepressant pharmacotherapy that included antidepressants and augmenting agents such as antipsychotics and mood stabilizers. All included studies were categorized into one of five groups according to how the antidepressant pharmacotherapy is addressed as part of a study design. Antianxiety medications were allowed by some studies; however, these medications were not assessed as part of the antidepressant strategy categorization as there is no evidence basis supporting their benefit as an augmentation agent.

Switch studies are those in which all patients discontinued their prior antidepressant treatment before initiating their next step treatment. Other studies allowed patients to continue their prior antidepressant pharmacotherapy and initiated next step treatment as an add-on or augmentation to their current treatment; these treatment strategies were termed *augmentation* strategies. In some augmentation studies, a small proportion of patients were not taking any psychotropic

medications before or during the trial. The inclusion of such patients is acknowledged in the study description.

A third set of studies used both switch and augmentation strategies and were categorized as *mixed*. Two types of mixed studies exist in the included literature. One group of studies encourages but does not require patients to discontinue their antidepressant medications, resulting in a study population that contains both switchers and augmenters in all study groups. Studies that allow different antidepressant medication strategies within research groups are called *mixed-within.* Other studies compare patients who *switch* to patients who *augment;* these studies use a mixed antidepressant medication strategy with between-group differences and are called *mixed-between*.

In another subset of studies, all patients initiated a new psychotropic medication at the same time in which active groups began the nonpharmacologic intervention. This strategy was termed *combination treatment*. Lastly, in a small group of studies, medications were not limited or initiated by the study (e.g., patients sought treatment as usual, which allowed them to change medications or continue the same regimen at the discretion of their treating doctor). This group of studies was described as having an *unlimited* psychotropic medication strategy. A small number of studies allowed (or disallowed) antidepressant medications and potential augmenting agents differently (e.g., antidepressants were discontinued but patients were allowed to continue antipsychotics); pharmacologic strategies of these studies are described in the text and summary tables. Details of each study's antidepressant medication strategy are provided in the evidence tables (Appendix D).

Disease Severity

Lastly, to enable us to examine differences based on disease severity, we grouped baseline scores into three categories: none to mild, moderate, and severe to very severe (Table 4).[55]

Table 4. Categories of depressive severity

Instrument	None/Mild	Moderate	Severe/Very Severe
HAM-D_{17}	≤ 13	14–19	≥ 20
HAM-D_{21}	≤ 15	16–22	≥ 23
HAM-D_{24}	≤ 18	19–26	≥ 27
MADRS	≤ 19	20–34	≥ 35
BDI	≤ 18	18–29	≥ 30
QID-SR	≤ 10	11–15	≥ 16

BDI = Beck Depression Inventory; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; QID-SR = Quick Inventory of Depressive Symptomatology—Self-Report.

Quality Assessment

To assess the quality (internal validity or risk of bias) of all included studies, we used predefined criteria based on those described in the AHRQ Methods Guide for Comparative Effectiveness Reviews (ratings: good, fair, poor).[56] Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer.

Elements of quality assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; overall and differential loss to followup; and the use of intention-to-treat analysis. We assessed observational studies based on the potential for selection bias (methods of selection of subjects and loss to followup), potential for measurement

bias (equality, validity, and reliability of ascertainment of outcomes), adjustment for potential confounders, and statistical analysis.

In general terms, a "good" study has the least bias, and results are considered to be valid. We rated studies that met all criteria as good quality. "Fair" studies presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our questions. A fair study is susceptible to some bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results. Studies that had a fatal flaw (defined as a methodological shortcoming that leads to a high probability of bias) in one or more categories were rated poor quality.

Poor-quality studies and reasons for that rating are presented in Appendix F. In this CER, we excluded poor-quality studies from our analyses if there were enough good or fair studies with significant findings. In some cases, a poor study may offer the only pertinent information about an important outcome or comparison, and we may comment on it in the relevant section of Results but it will not be included in summary tables there.

Applicability Assessment

Using the parameters for evaluation on guidance provided by AHRQ's Methods Guide for Comparative Effectiveness Reviews,[57] we evaluated the applicability of the studies included and evaluated in this CER. Applicability is essentially the generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out above, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of a Body of Evidence

We evaluated the strength of evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[56] Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four mandatory domains: risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships). As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.[56] We judged good-quality studies with strong designs to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction and had a narrow range. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. For active versus sham control comparisons, we graded the evidence as direct for general efficacy, which should not be interpreted as direct comparative effectiveness for the head-to-head comparisons considered in this report (e.g., rTMS vs. VNS, rTMS vs. ECT). For the main head-to-head comparisons for this report (ECT, rTMS, VNS, and psychotherapy), we graded evidence as being precise when results had a low degree of uncertainty. We had two separate

reviewers evaluate the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 5. We present our strength of evidence findings for TRD (Tier 1 studies) in our overview sections.

Table 5. Strength of evidence grades and their definitions

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in 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.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

Although we use the tiers as a guide to describe all the included evidence, our primary focus is on the populations with a Tier 1 TRD definition (two or more previous treatment failures). Some studies do not clarify whether failures occurred in a "current" episode or during one or more previous episode(s) (which can be characterized as over a "lifetime"). For that reason, our tiers may include a mix of studies that assess failing treatments in the current episode or failing treatments over a more extended period that may involve more than one episode. We highlight this distinction as appropriate. We also highlight other aspects of how treatment resistance, diagnosis, or severity of illness might vary.

For each KQ, we first present an overview of the particular comparison, including the strength of evidence findings for the Tier 1 studies. This section is followed by a key points section, which highlights important findings from the relevant comparisons, first for Tier 1 and then for Tiers 2 and 3. Finally, we present a detailed analysis section, which describes the individual studies, beginning with Tier 1 and followed by Tiers 2 and 3, in more detail. If possible, we report quantitative analyses as described below.

As described above, a complex and broad array of factors have the potential to shape the answers to the KQs. Throughout this report we synthesized the literature qualitatively.

If data were sufficient, we also augmented findings with quantitative analyses. We first quantitatively synthesized results for our primary focus, TRD (Tier 1) studies. Further, to assess how consideration of Tiers 2 and 3 affects Tier 1 findings alone, we also quantitatively synthesized results for Tiers 1, 2, and 3 combined to allow a comparison with Tier 1 alone.

We conducted meta-analyses of data for comparisons involving trials that were fairly homogenous in study populations, treatment intervention, and outcome assessments. For efficacy, we used three outcome measures:

1. The weighted mean difference of changes on the Hamilton Rating Scale for Depression (HAM-D). We chose this outcome measure to have an estimate of the actual difference in effect sizes between treatments.
2. The relative risk (RR) of being a responder (more than 50 percent improvement from baseline) on the HAM-D or the Montgomery-Åsberg Depression Rating Scale (MADRS) at study endpoint.

3. The RR of achieving remission on the HAM-D or MADRS at study endpoint. The HAM-D definition for the 17-item version was ≤ 8, and for the 21-item version was ≤ 10. For the MADRS, the remission definition was a score of ≤ 8. If a study used a slightly different definition for remission, this difference was noted in the study's summary table and was included if, in the authors' judgment, it did not substantially differ from the above.

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both a random and a fixed-effects model. We report the results from random effects models because, in all meta-analyses, the results from random and fixed effects models were very similar. If the RR was statistically significant, we calculated the number needed to treat (NNT) from the pooled RR or the pooled risk differences if variations in baseline risks were small.

We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias.

If meta-analyses were not possible but we deemed that an estimation of a treatment effect was of particular interest, we conducted descriptive statistics of the above-mentioned outcome measures. We calculated weighted means and 95 percent confidence intervals of changes on HAM-D or MADRS, and the percentages of responders and remitters for specific interventions or treatment strategies. The findings provide an estimate of the average, expected treatment effect for a specific intervention. Nevertheless, they have to be interpreted cautiously. Because of the lack of control groups, no general efficacy can be inferred from such results. Furthermore, the magnitude of treatment effects should not be compared across interventions.

Peer Review

This CER received external peer review from the TEP members and individuals who were experts in fields relevant to TRD (listed in the front matter) and from various stakeholder and user communities. The SRC managed the peer review process. If reviewers provided additional references to consider for inclusion in the final report, we reviewed all suggested references and included those that were appropriate and within the scope of this CER. We also addressed all comments and revised the report accordingly.

Results

Introduction

This chapter presents the results of our synthesis of the evidence on all six key questions (KQs, summarized in Table 6) about nonpharmacologic interventions for treating patients with treatment-resistant depression (TRD). To summarize, for all KQs except KQ 1, we are concerned with four major nonpharmacologic interventions: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT). As noted in Table 6, KQ 1b asks about pharmacologic interventions in patients who have two or more previous treatment failures.

Table 6. Key questions about treatment-resistant depression (TRD)

Key Questions
KQ 1a. Efficacy of nonpharmacologic interventions for acute-phase TRD (response or remission) KQ 1b. Efficacy of pharmacologic interventions for acute-phase TRD (response or remission), for patients with two or more prior treatment failures
KQ 2. Efficacy for maintaining response or remission (e.g., preventing relapse or recurrence)
KQ 3. Efficacy for acute-phase TRD as a function of particular symptom subtypes (e.g., catatonia or psychosis)
KQ 4. Harms of nonpharmacologic interventions (i.e., safety, adverse events, or adherence issues)
KQ 5. Efficacy or harms of nonpharmacologic treatments for selected subgroups defined by sociodemographic characteristics or coexisting conditions
KQ 6. Health-related outcomes of nonpharmacologic treatments (e.g., quality of life)

This chapter is organized as follows: first by KQ, second by intervention comparison, third by type of treatment failure (i.e., tier), and then by major depressive disorder (MDD) or MDD and bipolar study populations. In addition, according to the specifications from the Agency for Healthcare Research and Quality for comparative effectiveness reviews, within each KQ section, we present an overview, then key points, and finally detailed analyses. Finally, as explained in the Methods chapter, we graded the strength of evidence for all major comparisons and outcomes. We provide our readers with the strength of evidence findings for TRD (Tier 1 studies) in the Overview sections for each KQ.

We focus in this chapter chiefly on trials, which can be head-to-head investigations or trials with control arms involving sham procedures or, for behavioral interventions, various forms of "usual care" that can include physician (psychiatrist) visits, medications, or both. For KQ 4 on harms, we also include observational studies. Evidence tables for all studies are presented in Appendix E.

We include information only on studies for which our quality ratings were good or fair; most studies were rated fair, so we specifically call out quality ratings only for good trials or studies. Poor-quality studies are listed in Appendix G; in the very few cases in which a poor-quality study may have had the only relevant information on a major comparison or outcome, we will cite information about statistically significant findings in the detailed analysis text. Summary tables in the detailed analyses subsections have only good or fair quality studies.

We identified 2,444 citations from searches across databases. Additionally, we detected 310 articles from manually reviewing the reference lists of pertinent review articles. Figure 4 documents the disposition of the 79 articles in this review. Of the total 2,754 abstracts screened, 1,896 citations were excluded. Working from 858 articles retrieved for full review, 779 were excluded at this stage (Appendix D). Of the studies excluded at the full review, 269 were excluded for no or wrong comparison, 249 were excluded for including the wrong population, 137 were excluded for wrong publication type, 53 were excluded due to the analysis of outcomes

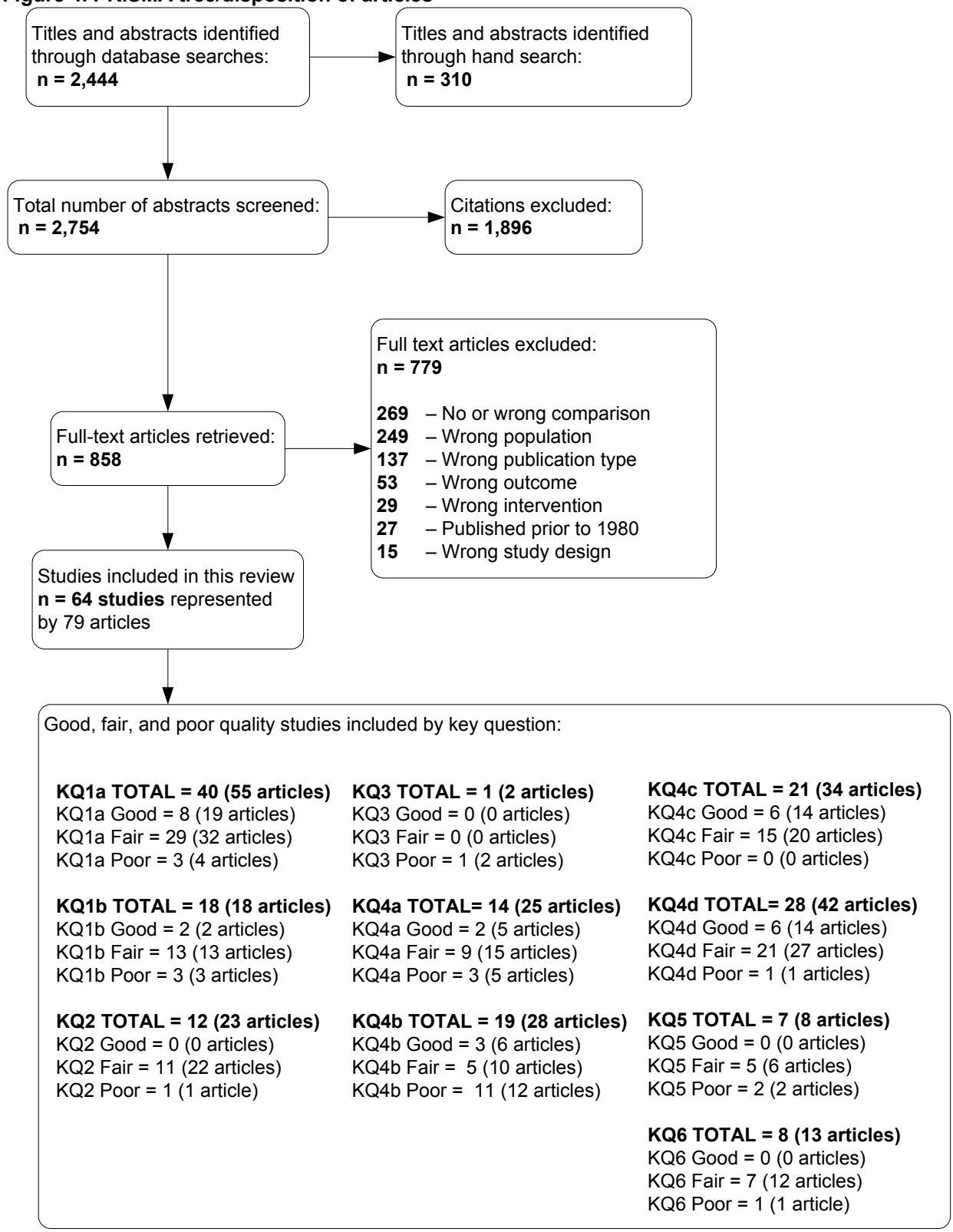
not of interest, 29 were excluded for performing analysis on an intervention not of interest, 27 were excluded for a publishing date prior to 1980, and 15 were excluded because the study was the wrong study design. We included 79 published articles reporting on 64 studies: 62 randomized controlled trials (RCTs) (77 articles) and 2 observational studies (2 articles). Evidence tables for included studies, by key question, can be found in Appendix E.

Of the 79 included articles, 17 (22 percent) were supported by pharmaceutical or device manufacturers; 48 (61 percent) were funded by governmental or independent funds. We could not determine the source of support for 14 (17 percent) studies.

Of the included studies, there were 17 head-to-head RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a non-pharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTs of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RTCs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). We excluded eight studies (eight articles) because of poor quality.

Most included studies were relevant for more than one KQ. For KQ 1a a total of 40 studies (55 articles) were included. Of these studies, 8 (19 articles) were rated as good and 29 (32 articles) were rated fair quality for internal validity. KQ 1b included 18 studies (18 articles), of which 2 studies (2 articles) were rated as having good internal validity and 13 studies (13 articles) were rated as having fair internal validity. For KQ 2, a total of 12 studies (23 articles) were included. Of these studies, none were rated as good. Eleven studies in KQ 2 (22 articles) were rated as fair quality for internal validity. No studies with good or fair internal validity were identified for KQ 3. For KQ 4a, a total of 14 studies (25 articles) were included. Of these studies, two studies (five articles) were rated as good. Nine studies in KQ 4a (15 articles) were rated as fair quality for internal validity. KQ 4b included 19 studies (28 articles), of which 3 studies (6 articles) were rated as having good internal validity and 5 studies (10 articles) were rated as having fair internal validity. For KQ 4c, a total of 21 studies (34 articles) were included. Of these studies, 6 studies (14 articles) were rated as good. Fifteen studies in KQ 4c (20 articles) were rated as fair quality for internal validity. KQ 4d included 28 studies overall (42 articles), of which 6 studies were good (14 articles) and 21 studies (27 articles) were rated as fair. KQ 5 included a total of seven studies (eight articles). No studies were rated as good, and five studies (six articles) were rated as fair. For KQ 6, a total of 8 studies (13 articles) were included, 7 of which were rated as having fair internal validity, while no studies were rated as having good internal validity.

Figure 4. PRISMA tree/disposition of articles



*Articles were included for more than one KQ

Reasons for exclusion were based on eligibility criteria or methodological criteria. Studies that originally met eligibility criteria but were later rated as poor quality for internal validity are located in Appendix E. Eight distinct studies were excluded from consideration for any of the KQs because of poor quality. Eleven studies were included in the review that were rated as fair or good quality and included certain key questions (e.g., KQ 1a), but were rated as poor for other key questions and hence excluded (e.g., KQ 4b). For KQ 1a, three studies (four articles) were rated as poor. KQ 2, KQ 3, and KQ 6 each rated one study as poor. KQ 1b excluded three studies for poor internal validity. Of the studies applicable to KQ 4a, three studies (five articles) were rated as having poor internal validity. KQ 4b excluded 11 studies (12 articles) for poor internal validity. For KQ 4c, no poor studies were identified. One study was rated as having poor internal validity in KD 4d. KQ 5 excluded two studies (two articles) for poor internal validity. The main reason for rating as poor of studies was due to poor reporting of methodology.

Key Question 1: Organization of Results

The presentation of KQ 1, which deals only with efficacy and effectiveness of interventions undertaken in acute phase treatment, is complex. Such clinical outcomes are one of a number of variables guiding the selection of therapy. Other considerations in acute phase treatment—such as effectiveness for subgroups, harms, and other health-related outcomes like quality of life—are addressed by KQs 3 through 6. KQ 2, in contrast, assesses the role of treatment selection in maintaining response or remission during continuation phase treatment.

Our primary focus is on comparisons of nonpharmacologic interventions—ECT, rTMS, VNS, and psychotherapy—presented as KQ 1a. We present evidence that stratifies first by which interventions are being compared, then by tier, and then by whether the population was MDD-only or MDD/bipolar mix. Within each tier, we attempt to assess the effect on outcomes of key PICOTS (patient population, intervention, comparison, outcome, and timeframe) elements: whether the population is MDD versus MDD/bipolar mix; whether treatment failure is required in the current episode; the level of depressive severity; treatment characteristics (e.g., number of treatment sessions, treatment location); and treatment strategy (e.g., whether patients switched to a new treatment or added a new treatment to augment their current treatment). We focus on Tier 1 TRD data first, and then we consider potentially relevant data from Tiers 2 and 3. We begin by reviewing this head-to-head literature.

Given the limited number of head-to-head comparisons available, we also review the nonpharmacologic interventions versus control to assess whether we might be able to extend our analyses through indirect comparison. Such indirect analyses require a suitable number of comparisons with placebo or sham groups across the interventions.

Next, in KQ 1b, we compare nonpharmacologic to pharmacologic interventions. We present the evidence in a similar order. First, we review head-to-head nonpharmacologic versus pharmacologic comparisons. Second, we review available pharmacologic versus pharmacologic literature addressing response to antidepressant management to provide a comparison of what might be expected with a next-step pharmacologic treatment for TRD. These comparisons involve only MDD-only, Tier 1 study populations. In reviewing the pharmacologic literature, we attempt to identify adequate control groups that would allow us to generate indirect measures of the relative outcomes of pharmacologic versus control interventions that we can compare to the nonpharmacologic effect sizes. Throughout KQ 1, we provide a qualitative synthesis of the evidence; this synthesis is paired with a quantitative analysis of this data when an adequate number of studies are identified.

Our main outcomes of interest are changes in depressive severity, rates of response, and rates of remission. Most studies report these outcomes using a version of the Hamilton Rating Scale for Depression (HAM-D), so we focus on this result; however, in the absence of HAM-D scores, we used Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), or Quick Inventory of Depressive Symptomology (QIDS-SR) scores. In Table 7, information is provided for these scales. For each outcome, we report the results of appropriate statistical tests comparing results between groups. All statistics are based on an intention-to-treat analysis unless otherwise specified. In studies in which the mean change in depression severity or proportion of responders or remitters is not reported but in which sufficient information is provided to calculate these variables, we made the calculations and include this information in the tables. To assist the reader making comparisons between studies, the proportion of responders and remitters is shown as a function of the number of participants randomized (i.e., an intention-to-treat [ITT] analysis); statistical analyses calculated using a completers, per-protocol, or modified-ITT analysis are identified as such in the summary tables. We also categorized each population for depression severity using the chart described in Table 4 of the Methods section. We consider only studies assessed as good or fair quality.

Table 7. Abbreviations and full names of diagnostic scales and other instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by
BDI	Beck Depression Inventory	0-63	Decrease
HAM-D_{17}	Hamilton Rating Scale for Depression – 17 item	0-52	Decrease
HAM-D_{21}	Hamilton Rating Scale for Depression – 21 item	0-64	Decrease
HAM-D_{24}	Hamilton Rating Scale for Depression – 24 item	0-75	Decrease
HAM-D_{25}	Hamilton Rating Scale for Depression – 25 item	0-52	Decrease
MADRS	Montgomery-Asberg Depression Rating Scale	0-60	Decrease
QID-SR	Quick Inventory of Depressive Symptomology – Self Report	0-27	Decrease

Key Question 1a: Nonpharmacologic Interventions—Overview of Head-to-Head Comparisons

Six head-to-head comparisons were available, four comparing ECT with rTMS and two comparing ECT with a combination of ECT plus rTMS (Table 8).

Table 8. Number of good- and fair-quality studies by comparison, tier, and diagnostic mix for KQ 1a

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT versus rTMS	Tier 1 (≥ 2 treatment failures)	1	0
ECT versus rTMS	Tier 2 (≥ 1 treatment failures)	1 additional	0
ECT versus rTMS	Tier 3 (probable treatment failures)	0	2 additional
ECT versus ECT plus rTMS	Tier 1 (≥ 2 treatment failures)	1	0
ECT versus ECT plus rTMS	Tier 3 (probable treatment failures)	1 additional	0

ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation

Of the four studies (reported in six articles) that compared ECT with rTMS,[58-63] only one was in a Tier 1 MDD population.[58] Both this study and the single Tier 2 MDD study[59] found no significant differences between groups. However, a good-quality Tier 3 MDD/bipolar mix study found a greater change in depressive symptomatology and higher response and remission rates in the ECT group.[61,63] A second Tier 3 study rated fair supported these results showing higher response and remission rates in the ECT group.[60]

Of the two studies comparing ECT with a combination of ECT and rTMS, both were in an MDD population; one was in a Tier 1 study[64] and the other was Tier 3.[65] These two studies showed no difference in outcome between treatments.

All studies included patients with severe depression, and none required a failure in the current episode, preventing an assessment of the role of these variables on outcome. For studies comparing ECT with rTMS, the two Tier 3 studies favored ECT while the Tier 1 and 2 studies showed no difference in outcomes, but the limited number of studies limit observation of any true pattern.

We could not assess how type of treatment strategy affected outcomes because of the limited number of studies and the multiple types of treatment strategies used. Studies varied by whether the trial tested interventions as a switch strategy (switching from the current failed treatment to a new strategy),[58,59,65,66] or an augmentation strategy (adding the new intervention to the current regimen).[60-63] Finally, some studies compared combinations of treatments (such as ECT versus ECT plus rTMS).[64,65]

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. One study provides a low strength of evidence that there were no differences in depressive severity, response rates, or remission rates between switching to ECT versus switching to rTMS (Table 9).[58] Similarly, a second study provides a low strength of evidence that there were no differences in changes in depressive severity or between groups augmenting with ECT or with ECT plus rTMS (Table 10).[64] Results from both studies are limited by a small sample size.

Table 9. Strength of Evidence: Efficacy of ECT versus rTMS

Outcome	Number of Studies; Subjects	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low
Response	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low
Remission	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Table 10. Strength of Evidence: Efficacy of ECT plus rTMS versus ECT

Outcome	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 22	Medium RCT 1 fair	Unknown	Indirect (compares combination to ECT rather than rTMS to ECT)	Imprecise	No significant difference Low
Response	0; 0	—	—	—	—	—
Remission	1; 22	Medium RCT 1 fair	Unknown	Indirect (compares combination to ECT rather than rTMS to ECT)	Imprecise	No significant difference Low

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Key Question 1a: Nonpharmacologic Interventions–Key Points of Head-to-Head Comparisons

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Two fair MDD-only studies, one Tier 1[58] and one Tier 2,[59] found no differences in changes in depressive symptomatology, response, or remission. However, a good-quality Tier 3 MDD/bipolar mix study found a greater change in depressive symptomatology and higher response and remission rates in the ECT group;[61,63] a second Tier 3 study rated fair supported these results, showing higher response and remission rates in the ECT group.[60]

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Two fair studies, one Tier 1 MDD-only[64] and one Tier 3 MDD-only,[65] found no difference in changes in depressive symptomatology, response, or remission.

Key Question 1a: Nonpharmacologic Interventions—Detailed Analysis of Head-to-Head Comparisons

Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

One trial comparing ECT with rTMS was identified in Tier 1 (Table 11).

Table 11. Efficacy of ECT versus rTMS: Tiers 1–3

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Rosa et al., 2006[58] 2–4 weeks of active treatment (after week 2, rTMS non-responders withdrawn with LOCF) Tier 1: Did not require failure in the current episode Fair	**ECT (n = 20)** % bilateral NR, mean number of sessions 10 (1.5) **rTMS (n = 22)** High frequency (10Hz), up to 20 sessions, 2500 pps (slightly outside safety guidelines) **Treatment Strategy** Switch **Definitions** Remission Ham-D_{17} ≤ 7	**Mean number of failed antidepressant trials:** ECT: NR rTMS: NR **Baseline Depression:** HAM-D_{17}, mean (SD) ECT: 32.1 (5.0)* rTMS: 30.1 (4.7)* *completers analysis ECT: n = 15 rTMS: n = 20	**HAM-D_{17}** Change, mean (SD): NR *P* = 0.86	**HAM-D_{17}** Response, n (%) ECT: 6 (20) rTMS: 10 (45) *P* = 0.35 Remission, n (%) ECT: 3 (15) rTMS: 2 (9) *P* = 0.65
Grunhaus et al., 2003[59] 4 weeks for rTMS; ECT was at physician discretion, all reported pts included in analysis Tier 2: Did not require failure in the current episode Fair	**ECT (n = 20)** 35% bilateral, mean sessions = 10.25 (3.1) **rTMS (n = 20)** High frequency, 20 sessions **Treatment Strategy** Switch **Definitions** Response defined as a decrease ≥ 50% or HAM-D_{17} score ≤ 10 and a GAF rating ≥ 60 Remission defined as HAM-D_{17} ≤ 8	**Number of failed antidepressant trials:** % with ≥ 2 failed ECT: 60 rTMS: 65 **Baseline Depression:** HAM-D_{17}, mean (SD) ECT: 25.5 (5.9) rTMS: 24.4 (3.9)	**HAM-D_{17}** Change, mean (SD) ECT: -12.3 rTMS: -11.1 *P* = NS	**HAM-D_{17}** Response, n (%) ECT: 12 (60) rTMS: 11 (55) *P* = NS Remission, n (%) ECT: 6 (30) rTMS: 6 (30) *P* = NS
Hansen et al., 2010[60] 3 weeks, ITT Did not require failure in the current episode Tier 3—referred for ECT Fair	**ECT (n = 30)** 100% unilateral, 9 sessions **rTMS (n = 30)** Low frequency, 15 sessions **Treatment strategy** Augmentation Discontinued antiepileptics prescribed as mood stablizers. Low-dose zopiclone or zopidem if needed for sleep **Definitions** Partial remission HAM-D_{17} ≤ 12	**Diagnosis** Bipolar (%) ECT: 13.3 rTMS: 13.3 **Number of failed antidepressant trials:** Mean (SD) ECT: NR rTMS: NR **Baseline Depression:** HAM-D_{17}, median (range) ECT: 24 (16-34) rTMS: 24 (14-38)	**HAM-D_{17}** Change, mean (SD) Reported in graph only	**HAM-D_{17}** Response, n (%)* ECT: 17 (57) rTMS: 6 (20) Response rate difference = 0.37 (0.14-0.59) Partial Remission, n (%)* ECT: 16 (53) rTMS: 8 (27) Partial Remission rate difference = 0.26 (0.03-0.51)

Table 11. Efficacy of ECT versus rTMS: Tiers 1–3 (continued)

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
McLoughlin et al., 2007,[61] Eranti et al., 2007,[62] and Knapp et al., 2008[63] End of treatment (at clinician's discretion for ECT group, 3 weeks in rTMS), mITT Did not require failure in the current episode Tier 3—referred for ECT Good	**ECT (n = 22)** 82% bilateral, mean session 6.3 (2.5) **rTMS (n = 24)** High frequency, 15 sessions **Treatment strategy** Augmentation **Definitions** Remission defined as ≤ 8	**Diagnosis** Bipolar (%) ECT: 9.1 rTMS: 8.3 **Number of failed antidepressant trials:** Mean (SD) ECT: 2.5 (1.4) rTMS: 2.4 (1.0) **Baseline Depression:** HAM-D_{17}, mean (SD) ECT: 24.8 (5.0) rTMS: 23.9 (7.0)	**HAM-D_{17}** Change, mean (SD)* ECT: -14.1 rTMS: -5.4 *P* = 0.017 *only pts with post-baseline assessment ECT: n = 22 rTMS: n = 23	**HAM-D_{17}** Response, n (%)* ECT: 13 (59.1) rTMS: 4 (17.4) *P* = 0.005 Remission, n (%)* ECT: 13 (59.1) rTMS: 4 (17.4) *P* = 0.005

AD = antidepressant; ECT = electroconvulsive therapy; HAM-D_{17} = 17-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; n = number; NR = not reported; *P* = p-value; pps = pulses per session; pts = patients; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD-Only

One trial directly compared 4 weeks of ECT (n = 20 patients) to high-frequency rTMS (n = 22 patients) (Table 11).[58] The mean baseline HAM-D_{17} for treatment completers was 32.1 (SD 5.0) (ECT; n = 15 patients) and 30.1 (standard deviation [SD] 4.7) (rTMS; n = 20 patients), indicating that the groups were severely depressed. ECT was initially unilateral, and it was switched to bilateral if there was no response after 2 weeks; the mean number of treatments was 10. If rTMS patients had not responded after 2 weeks, they exited the study with their last observation carried forward. The treatment strategy was a switch. ITT analyses indicated no difference between the likelihood of response with ECT versus rTMS (20% vs. 45%, *P* = 0.35), nor was there any difference between the likelihood of remission (15% vs. 9%, *P* = 0.65).

MDD/Bipolar

There were no eligible studies.

Tier 2: Patients With one or More Treatment Failures

One trial comparing ECT with rTMS was identified in Tier 2 (Table 11).

MDD-Only

One additional study was captured considering Tier 2 (Table 11).[59] This trial directly compared up to 4 weeks of ECT (n = 20 patients) with 20 sessions of high-frequency rTMS (n = 20 patients) after patients were switched from antidepressant pharmacotherapy (). Patients were severely depressed (mean HAM-D_{17} for ECT group 25.5 [SD 5.9] and for rTMS group 24.4 [SD 3.9]). For the ECT group, patients began with unilateral treatment but were switched to bilateral treatment if response was limited. Although rTMS treatment totaled 20 sessions, ECT treatment continued until the treating physician assessed that a therapeutic response had been obtained or no further benefit was expected. The authors' analyses accounted for all patients who were randomized. At the end of treatment, ECT and rTMS patients did not differ significantly in either

depressive severity (-12.3 vs. -11.1), the response rate (60% vs. 55%), or the remission rate (30% vs. 30%).

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

Two trials comparing ECT with rTMS were identified in Tier 3 (Table 11).[60-63]

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two studies were identified for Tier 3 (Table 11).[60-63] The first study was reported in three articles and was the only good trial involving a head-to-head comparison. Investigators used an augmentation strategy to compare outcomes following 2–3 weeks of ECT (n = 22 patients) versus 3 weeks of rTMS (n = 24) in a group of patients referred for ECT. Although failure of a prior antidepressant treatment was not a selection criterion for the study, the mean number of previous antidepressant failures was approximately 2.5 in each treatment group. The ECT group had 9.1 percent with bipolar disorder (n = 2), and the rTMS groups had 8.3 percent (n = 2) with bipolar disorder. Patients were severely depressed at baseline (mean HAM-D_{17} = 23.9 [SD 7.0] for rTMS and 24.8 [SD 5.0] for ECT). In a modified ITT analysis, ECT patients had better outcomes in all depression domains recorded at the end of treatment. Compared to the rTMS group, those receiving ECT experienced a greater decrease in depressive severity (mean HAM-D_{17} change -14.1 vs. -5.4, $P = 0.017$) and higher rates of both response and remission (59.1% vs. 17.4%, $P = 0.005$ for each, as all who responded also remitted).[60]

A second Tier 3 study comparing ECT with rTMS was rated fair.[60] Investigators used a mostly augmentation strategy but required patients to discontinue antiepileptics (when used as mood stabilizers) and benzodiazepines. Patients referred for ECT were randomized to 3 weeks of ECT (n = 30) or rTMS (n = 30). Both groups were severely depressed at baseline (median HAM-D_{17} = 24 [range 16–34] for ECT and 24 [14–38] for rTMS). In an ITT analysis, ECT patients had better outcomes in all depression domains recorded at the end of treatment. Compared to the rTMS group, the ECT group experienced a higher rate of response (57% vs. 20%, rate difference: 0.37 [0.14–0.59]) and partial remission (defined as HAM-$D_{17} \leq 12$: 53% vs. 27%, rate difference: 0.26 [0.03–0.51].

Tiers 1-3: Combined Results

Although the two Tier 1 studies alone provided limited evidence of no difference between ECT and rTMS, consideration of Tiers 2 and 3 added three studies with varying results: one Tier 2 study showed no difference between ECT and rTMS and two Tier 3 studies favored ECT over rTMS.

In considering studies from all three tiers, then, two fair studies, one Tier 1 and one Tier 2, found no differences between groups in change in depressive severity, response, or remission;[58,59] two Tier 3 studies (one good, one fair) found that ECT resulted in greater efficacy across measures.[61-63] With only four studies identified for this comparison, it is difficult to assess

what study design, participant, or treatment characteristics may have contributed to different results in both intervention efficacy and between-group comparisons.

Although the good study indicating greater efficacy for ECT was identified in Tier 3, the mean number of failed trials (N = 2.4–2.5) indicates substantial overlap with patients included in Tier 1 and Tier 2 studies.[61-63] These data were not reported for the second Tier 3 study.[60] Baseline characteristics reported in the Tier 2 study also show overlap with Tier 1 populations, with more than 60 percent of participants failing two or more antidepressant treatment trials.[59] None of the studies comparing ECT with rTMS required an antidepressant failure in the current episode. Average baseline depression scores indicate severe depression for all study populations. In the two studies allowing bipolar patients, the numbers of patients with this diagnosis were small and patients were equally distributed between treatment groups.[60-63]

Both studies finding no differences used switch strategies[58,59] while the two studies showing greater efficacy for ECT used an augmentation strategy.[60-63] Studies employed slightly different intervention methodologies using either high[58,59,61-63] or low frequency rTMS[60] and unilateral[60] or bilateral[58,59,61-63] ECT, further complicating comparisons between studies. All studies were 2 to 4 weeks in duration.

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

One trial comparing ECT with ECT plus rTMS was identified in Tier 1 (Table 12).[64]

Table 12. Efficacy of ECT versus ECT plus rTMS: Tiers 1–3

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Pridmore, 2000[64] 2 weeks of treatment Did not require failure in the current episode Tier 1 Fair	**ECT (n = 11)** 100% unilateral, 6 sessions **ECT plus rTMS (n = 11)** ECT: 100% unilateral (day 1), plus high-frequency rTMS: (days 2-5) Repeated in week 2 **Treatment Strategy** Primarily augmentation (4 patients not on AD at start). ADs and mood stabilizers continued but other psychotropics discontinued **Definitions** Remission HAM-D_{17} < 9	**Mean number of failed antidepressant trials:** ECT: NR ECT+rTMS: NR **Baseline Depression:** HAM-D_{17}, median ECT: 30 ECT+rTMS: 28	**HAM-D_{17}** Change, median ECT: -23 ECT+rTMS G2: -20 *P* = 0.6	**HAM-D_{17}** Remission, n (%) ECT: 6 (54.5) ECT+rTMS G2: 6 (54.5) *P* = NR

Table 12. Efficacy of ECT versus ECT plus rTMS: Tiers 1–3 (continued)

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Chistyakov et al., 2005[65] 3 weeks, all reported patients included Did not require failure in the current episode Tier 3: referred for ECT Fair	**ECT plus sham (n = 10)** Bilateral ECT (2 days a week) plus sham rTMS (4 days a week) **ECT plus rTMS (n = 12)** Bilateral ECT (2 days a week) plus low frequency rTMS (4 days a week) **Treatment strategy** Switch	**Mean number of failed antidepressant trials:** ECT + sham: NR ECT+rTMS: NR **Baseline Depression:** HAM-D mean reported in graph only	**HAM-D_{NR}** Change, mean (SD) ECT+sham: NR ECT+rTMS: NR *P* > 0.05	**HAM-D_{NR}** Response, n (%) Overall: 19 (86) ECT+sham: NR ECT+rTMS: NR *P* = NS

AD = antidepressants; ECT = electroconvulsive therapy; HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{NR} = Hamilton Depression Scale; n = number; NR = not reported; NS = not significant; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD-Only

One trial directly compared 2 weeks of unilateral ECT (n = 11 patients) to a combination of 1 day of unilateral ECT followed by 4 days of high-frequency rTMS (n = 11 patients).[64] Patients were severely depressed at entry (median HAM-D_{17} for ECT group = 30 and for ECT plus rTMS group = 28). For the majority of patients, this trial tested an augmentation strategy. However, four patients (two in each group) were not taking any antidepressant medication at study entry, and patients were allowed to continue any mood stabilizers they were taking (one in each group). ITT analyses showed no clear difference in outcomes between the two groups. Specifically, there was no difference in change in depressive severity (-23 vs. -20, *P* = 0.6) or remission rates (54.5% vs. 54.5%, *P* = not reported).

MDD/Bipolar

There were no eligible studies.

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

One trial comparing ECT with ECT plus rTMS was identified in Tier 1 (Table 12).[65]

MDD-Only

Following discontinuation of antidepressant pharmacotherapy (switch strategy), a 3-week study compared 6 sessions of bilateral ECT plus 12 sessions of low frequency rTMS (n = 12) versus 6 sessions of bilateral ECT plus 12 sessions of sham rTMS (n = 10).[65] Depressive severity was not reported in text, but figures indicate HAM-D (NR) was above 40 for each group, suggesting very severe depression. The treatment strategy was a switch, and no other psychotropic medications were allowed. All patients were included in the final analysis. There was no clear difference in response rates between ECT plus rTMS versus rTMS alone (data not reported, *P* = NS).

MDD/Bipolar mix

There were no eligible studies.

Tier 1-3 Combined Results

Two fair studies found no differences between groups in change in depressive severity, response, or remission.[64,65] With only two studies identified for this comparison, it is difficult to assess how study design, participant, or treatment characteristics may have affected treatment efficacy; furthermore, one of the two studies did not report specific data points impeding additional analysis.

Overall, studies appeared similar with the exception of tier. One study fell into Tier 1[64] and one into Tier 3[65] with no information provided regarding the average number of antidepressants failed prior to study entry for the Tier 3 study.[65] Neither study required a failure in the current episode. All patients were diagnosed with MDD and the average baseline depression scores indicate severe depression for both study populations. Dosing strategies for the combination groups in both studies were similar with patients receiving one to two sessions of ECT and four sessions of rTMS per week. ECT strategies were also similar with patients receiving 2–3 ECT sessions per week. One study used high-frequency rTMS and unilateral ECT[64]; the other used low frequency rTMS and bilateral ECT.[65] Lastly, one study was 2 weeks and the other was 3 weeks.

Key Question 1a: Nonpharmacologic Interventions—Overview of Active Versus Control Comparisons

A total of 31 studies comparing an active nonpharmacologic intervention with a sham or control group were identified (Table 13), providing a total of 4 distinct comparisons: 2 comparing ECT with sham,[67,68] 24 comparing rTMS with sham,[18,69-92] 4 comparing psychotherapy with control,[93-97] and 1 comparing VNS with a control group.[98] The small number of studies within some comparisons (i.e., ECT = two studies, VNS = one study, psychotherapy = four studies) and the clinical heterogeneity between study populations (e.g., severity of depression, previous antidepressant failures) did not allow for indirect comparisons of nonpharmacologic interventions.

Table 13. Number of studies included by comparison and tier for KQ 1a active versus control comparisons

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT versus sham	Tier 3 (probable)	1	1
rTMS versus sham	Tier 1 (≥ 2 failures)	10	5
rTMS versus sham	Tier 2 (≥ 1 failures)	4 additional	2 additional
rTMS versus sham	Tier 3 (probable)	0	3 additional
Psychotherapy versus control	Tier 2 (≥ 1 failures)	4 additional	0
VNS versus control	Tier 1 (≥ 2 failures)	0	1 additional

MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; TAU = treatment as usual; VNS = vagus nerve stimulation

There were no Tier 1 or Tier 2 studies comparing ECT to sham. The 2 studies comparing ECT to sham stimulation were Tier 3 studies that provided no indication of the number of prior antidepressant failures, and both reported treatment completers analyses rather than intention-to-treat. Both studies found better outcomes for the ECT group.[67,68]

A sufficient number of studies comparing rTMS to sham stimulation allowed for some comparisons across variables. Results for Tier 1 versus Tiers 1–3 combined were consistent and generally consideration of all tiers provided more conservative point estimates with narrower

confidence intervals, suggesting that the tier results might be reasonably combined. Results for MDD-only and MDD/bipolar mix populations were in the same direction and of similar magnitude, suggesting that combining results from these two populations was reasonable. A limited number of studies within comparisons restricted analysis and prevented assessment of whether outcomes differed by depressive severity, treatment strategy, or treatment characteristics, or whether failure in the current episode was required.

Four Tier 2 MDD-only studies compared psychotherapy to control.[93-97] For the third comparison, one good study reported in two articles[95,96] and two fair studies[93,97] supported greater outcomes for patients in psychotherapy compared to a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.[94] Unlike the first three studies,[93,95-97] the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning.[94]

The single study comparing VNS to a control was in a Tier 1 MDD and <20 percent bipolar population.[98] This study included patients with a higher level of treatment resistance than other studies comparing interventions in TRD populations. Considering change in HAM-D_{24} and response outcomes only, patients in the VNS groups did not improve significantly more than patients in the control group.

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. A total of 15 different Tier 1 trials compared rTMS versus sham control for at least one of the three outcomes (Table 14). For changes in depressive severity, 14 rTMS versus sham control studies involving 497 participants provide a high degree of evidence that rTMS produces a greater decrease in depressive severity.[18,69-73,75-82] Studies that did not report significant differences had small samples. A random effects meta-analysis of 11 Tier 1 studies indicated that rTMS produces a decrease in HAM-D depressive severity of more than 5 points relative to sham control.

Table 14. Strength of Evidence: Efficacy of rTMS versus sham—Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	14; 497	Low RCT 3 good 11 fair	Consistent	Indirect	Precise	rTMS > sham High
Response	12; 471	Low RCT 3 good 9 fair	Consistent	Indirect	Precise	rTMS > sham High
Remission	5; 223	Low RCT 2 good 3 fair	Consistent	Indirect	Precise	rTMS > sham Moderate

RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

For response rates, 12 rTMS versus sham control studies involving 471 participants provided a high degree of evidence that rTMS is more likely to produce a response than sham control.[18,69-72,74-77,80-82] A random effects meta-analysis of 11 Tier 1 studies shows that patients receiving

rTMS are more than three times as likely to achieve a depressive response as patients receiving sham control.

For remission rates, five rTMS versus sham control studies involving 223 patients provided moderate strength of evidence that rTMS produces greater remission rates than rTMS (Table 14).[18,74,77,81] A random effects meta-analysis of five Tier 1 studies shows that patients receiving rTMS are more than six times as likely to achieve remission as patients receiving sham control.

In the only other Tier 1 comparison, one good-quality VNS versus sham control study in an MDD/bipolar mix population involving 222 participants provides low evidence that neither a change in depressive severity nor response rates following VNS substantially differ from a sham control (Table 15).[98]

Table 15. Strength of Evidence: Efficacy of VNS versus Sham—Tier 1

Outcome	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 222	RCT Low 1 good	Unknown	Indirect	Precise	No significant difference Low
Response	1; 222	RCT Low 1 good	Unknown	Indirect	Precise	No significant difference Low
Remission	0; 0	—	—	—	—	—

RCT = randomized controlled trial; VNS = vagus nerve stimulation

Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Key Points of Active Versus Control Comparisons

Active versus control comparisons were also limited, and the small number of studies within comparisons prevented an indirect meta-analytic synthesis. Comparisons of an active nonpharmacologic intervention compared to a sham or control group were available for 4 distinct comparisons: 2 comparing ECT with sham,[67,68] 24 comparing rTMS with sham,[18,69-92] 4 comparing psychotherapy with control,[93-97] and 1 comparing VNS with a control group.[98] The small number of studies within some comparisons (i.e., ECT = two studies, VNS = one study, psychotherapy = four studies) and the clinical heterogeneity between study populations (e.g., severity of depression, previous antidepressant failures) did not allow for indirect comparisons of nonpharmacologic interventions.

Electroconvulsive Therapy Versus Sham

We identified no ECT versus sham studies conducted in a Tier 1 population. Two Tier 3 studies comparing ECT with sham stimulation were identified.[67,68] These two studies provided no indication of the number of prior antidepressant failures, and both reported treatment completers analyses rather than intention-to-treat. Both studies found greater outcomes for the ECT group.

Repetitive Magnetic Stimulation Versus Sham

For Tier 1, 10 MDD-only[69-78] and 5 MDD/bipolar mix studies were identified.[18,79-82] Three studies were deemed good quality,[18,77,80] and the remaining studies were assessed as fair. Though some studies did not report tests of statistical significance or had very small sample sizes, evidence generally supported the benefit of rTMS over sham for a decrease in depressive symptomatology and a greater likelihood of response and remission. Results from MDD-only and from MDD/bipolar mix studies were in the same direction and of similar magnitude, and results from combining these two populations did not substantially differ from MDD-only, suggesting that combining these two populations was reasonable. Meta-analyses in TRD (Tier 1) involving both MDD-only and MDD/bipolar mix populations indicated benefit for rTMS over sham. TRD patients treated with rTMS had significantly greater decreases in depressive symptomatology (decrease in HAM-D -5.74, 95% confidence interval [CI], -7.79 to -3.68). rTMS patients were also over 3 times as likely to respond (pooled relative risk for response 3.34, 95% CI, 1.92-5.82, which translates to a number needed to treat (NNT) of 5 [95% CI, 3-10]), and over 6 times as likely to remit (pooled relative risk for remission 6.12, 95% CI, 1.89-19.80), with a NNT of 4 (95% CI, 2-20).

Consideration of all tiers together for the combined MDD and MDD/bipolar mix populations provided results consistent with those from Tier 1 alone combined but with more conservative point estimates and narrower confidence intervals. The weighted mean difference in HAM-D depressive severity was -5.92 (95% CI, -8.15 to -3.70). Because sample sizes of individual studies were small and responses to placebo varied in the small control groups, the heterogeneity was high ($I^2 = 80\%$) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. The pooled relative risk indicated that patients receiving rTMS were more than twice as likely to respond as those receiving placebo (pooled relative risk 2.68, 95% CI, 1.52-4.70), which translates into an NNT of 5 (95% CI, 4-9). Remission rates also favored rTMS. The pooled relative risk for remission was 3.73 (95% CI, 1.23-11.30), which translates to a NNT of 6 (95% CI, 3-50).

This finding of the above clinical outcomes from Tiers 1, 2, and 3 reflecting what was found with Tier 1 alone held whether the population included was MDD-only, or MDD/bipolar mix, respectively. Findings addressing the remaining key PICOTS elements were limited. Three quarters of the Tier 1 studies used an augmentation strategy[18,69-75,79-81] while others (all MDD-only) used a switch (n = 1)[76] or a mixed strategy (n = 2).[77,78] There was no clear difference in outcome as a function of strategy, but the limited number of comparisons prevented a firm conclusion. The consideration of additional tiers of evidence did not affect this finding.

For the few Tier 1 studies, we were unable to detect clear differences by treatment characteristics (i.e., pharmacotherapy strategy, rTMS frequency, or treatment duration) through qualitative analysis due to other potentially confounding variables resulting from study design or participant characteristics. The consideration of additional tiers of evidence did not affect this finding.

For Tier 1, 1 study did not report baseline depressive severity,[79] 1 study focused on patients with moderate disease severity,[72] and the remaining 10 studies were on patients with severe depression. With little variation by depressive severity, we were unable to detect any differences by this variable. The consideration of additional tiers of evidence did not affect this finding.

Only three studies required a failure in the current episode, two in MDD-only[70,72] and one in MDD/bipolar mix,[79] with no differences in outcomes apparent, but the small number of studies

prevented a more formal analysis. The consideration of additional tiers of evidence did not affect this finding.

Finally, studies used a range of rTMS and sham stimulation parameters, treatment durations, and pharmacotherapy options, thereby confounding any analysis by treatment characteristics.

Psychotherapy Versus Control

Four Tier 2 studies, all involving a form of cognitive behavioral therapy, compared psychotherapy versus control. One good study reported in two articles,[95,96] and two fair studies[93,97] supported better outcomes for patients in psychotherapy compared with a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.[94] Unlike the first three studies,[93,95-97] the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning of the strategy.[94]

Vagus Nerve Stimulation Versus Sham

We identified only one study comparing VNS to sham, conducted in a Tier 1 MDD/bipolar mix population.[98] The majority of measures used by this study found no difference between VNS and sham on changes in depressive severity or rates of response and remission. Since only a single study was identified for this comparison, further assessment by key variables was not possible.

Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Active Versus Control Comparisons

Electroconvulsive Therapy Versus Sham

We identified two Tier 3 studies that compared ECT versus sham stimulation. Both studies comparing ECT to sham stimulation were in Tier 3 populations and were conducted in the early 1980s, limiting comparability to other studies in this report due to difference in antidepressant availability and study populations (e.g., no documented antidepressant failures).

Tier 1: Patients With two or More Treatment Failures

No study comparing ECT with sham in a Tier 1 population was identified.

Tier 2: Patients With one or More Treatment Failures

No study comparing ECT with sham in a Tier 2 population was identified.

Tier 3: Patients With Probable TRD

Two trials comparing ECT with sham stimulation were identified in Tier 3 (Table 16).

MDD-Only

One study in a population with "primary depressive illness" referred for ECT compared ECT (N = 13) with sham stimulation (N = 12).[67] Participants in this study had moderate depression at study entry (mean BDI, ECT 26.6 [2.8] and sham 24.1[3.5]). It is unclear what proportion of patients was on an antidepressant at study entry or had an antidepressant failure in the past. All

patients were prescribed amitriptyline during the trial. Based on a completers analysis, the ECT group had a larger mean decrease in depressive severity compared to the sham group (mean change in BDI, ECT, -15.8 versus sham: -1.9, $P < 0.002$).

MDD/Bipolar

One study in a population with "severe endogenous depression" referred for ECT compared ECT (N = 35) with sham stimulation (N = 35).[68] Participants in the study appear to have severe depression but these data are only reported in a graph. It is unclear what proportion of patients was on an antidepressant at study entry or had an antidepressant failure in the past. During the trial, patients were not prescribed an antidepressant medication. Based on a completers analysis, the ECT groups had a greater decrease in depressive severity compared with the sham group ($P < 0.01$).

Table 16. Efficacy of ECT versus sham: Tier 3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
West, 1981[67] 3 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	**ECT (n = 13)** Bilateral, 6 sessions **Sham (n = 12)** **Treatment strategy** Combination - unclear if patients taking an AD at baseline; 50 mg/d Amitriptyline during the trial	**Mean number of failed antidepressant trials:** ECT: NR Sham: NR **Baseline Depression** BDI, mean (SD) ECT: 26.6 (2.8) Sham: 24.1 (3.5)	**BDI** Change, mean (SD) ECT: -15.8 Sham: -1.9 $P < 0.002$ Completers ECT: N=11 Sham N=11	**BDI** Response NR Remission NR
Johnstone et al., 1980[68] 4 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	**ECT (n = 35)** Bilateral, 8 sessions **Sham (n = 35)** **Treatment strategy** Switch - unclear if patients taking an AD at baseline. No AD allowed during the trial	**Previous manic episodes:** Overall: 10% **Mean number of failed antidepressant trials:** ECT: NR Sham: NR **Baseline Depression** HAM-D_{17}, mean (SD) Reported in graph only	**HAM-D_{17}** Change, mean (SD) Reported in graph only *ECT versus sham $P < 0.01$ Completers ECT N = 31 Sham N = 31	**HAM-D_{17}** Response NR Remission NR

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tiers 1-3 Combined

Only Tier 3 studies were identified with results reported above. Given the limited data, we did not perform any quantitative syntheses.

Repetitive Magnetic Stimulation Versus Sham

Considering all tiers of evidence, 24 studies provided an rTMS versus sham comparison.[18,69-92]Fifteen were Tier 1 studies,[18,69-82] six were Tier 2 studies,[83-89] and three were Tier 3 studies.[90-92] Fifteen involved an MDD-only population[69-78] and nine had an MDD/bipolar mixture (< 20% with bipolar disorder).[83-87]

Tier 1: Patients With two or More Treatment Failures

Fifteen Tier 1 trials comparing rTMS with sham were identified in Tier 1.[18,69-82]

MDD-Only

Of the 10 Tier 1 MDD-only studies identified,[69-78,99] only 1 trial was good quality.[77,99]

Seven of these studies tested rTMS as an augmentation strategy (Table 17).[69-75] A 2-week augmentation study compared high-frequency rTMS (n = 12 patients) to sham rTMS treatment (n = 9 patients).[69] At entry, patients in the two groups were severely depressed (mean HAM-D_{25} item scores were 34.4 in the rTMS groups and 31.7 in the control group). Analysis was modified ITT. Patients in the rTMS group had a mean change in HAM-D_{25} severity of -11.75 versus -6.22 in the sham stimulation group (*P* = ns); the small sample size likely limited the power to detect a difference. Using the study's definition of response (> 30% in HAM-D_{25} item), 58.3 percent of rTMS patients responded compared to 22.2 percent of the sham stimulation group (*P* = not reported). Using a more standard definition of response as 50 percent or greater decrease (which we were able to calculate from study information), 22.2 percent of rTMS patients responded.

The largest augmentation study was a 2-week trial that compared high-frequency rTMS (n = 20 patients) to a sham control (n = 20 patients).[70] Participants' depression was severe (mean HAM-D_{21} in rTMS group = 27.1, and 25.6 in control). In an analysis of treatment completers, rTMS patients had a greater decrease in depressive severity (-7.05 vs. -1.77, *P* = 0.003). Including all participants, rTMS patients had a greater likelihood of response (25% vs. 5, *P* = NR) compared to control patients.

Table 17. Efficacy of rTMS versus Sham: Tier 1, MDD, augmentation strategies

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Boutros et al., 2002[69] 2 weeks Did not require failure in the current episode Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 9)** **Treatment strategy** Augmentation **Definitions** Response1 definition: >30% decrease in HAM-D_{25} Response2 definition: ≥50% decrease in HAM-D_{25} **calculated from table	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{25}, mean (SD) rTMS: 34.4 (10.1) Sham: 31.7 (4.9)	**HAM-D_{25}** Change, mean (SD) rTMS: -11.75 Sham: -6.22 *P* = NS	**HAM-D_{25}** Response1, n (%) rTMS: 7 (58.3) Sham: 2 (22.2) *P* = NR Response2, n (%)** rTMS: 3 (25.0) Sham: 2 (22.2) *P* = NR
Garcia-Toro et al., 2001[70] 2 weeks, completers analysis Required failure in the current episode Fair	**rTMS (n = 20)** High frequency, 10 sessions **Sham (n = 20)** **Treatment Strategy** **Augmentation**	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{21}, mean (SD) rTMS: 27.11 (6.65) Sham: 25.6 (4.92)	**HAM-D_{21}*** Change, mean (SD) rTMS: -7.05 (5.66) Sham: -1.77 (3.78) *P = 0.003* *all results based on completers (rTMS: n = 17, Sham: n = 18)	**HAM-D_{21}*** Response, n (%) rTMS: 5 (25) Sham: 1 (5) *P* = NR
Garcia-Toro et al., 2006[71] 2 weeks, all reported paticipants included in analysis Did not require failure in the current episode Fair	**rTMS-1 (n = 10)** High frequency plus low frequency, 10 sessions **rTMS-2 (n = 10)** Same as above, but with individually assessed location **Sham rTMS (n = 10)** Double winged coil angled at 45 degrees **Treatment strategy** Augmentation	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{21}, mean (SD) rTMS-1: 27.30 (4.97) rTMS-2: 25.00 (4.14) Sham: 25.10 (7.28)	**HAM-D_{21}** Change, mean (SD) rTMS-1: -7.2 rTMS-2: -6.9 Sham: -1.5 rTMS-1 plus rTMS-2 (-7.05) versus Sham, *P* = 0.048	**HAM-D_{21}** Response, n (%) rTMS-1: 2 (20) rTMS-2: 2 (20) Sham: 0 (0) *P* = NR
Kauffmann et al., 2004[72] 2 weeks Did not require failure in the current episode Fair	**rTMS (n = 7)** Low frequency, 10 sessions **Sham (n = 5)** **Treatment Strategy** Augmentation, pts encouraged to discontinue mood stablizers **Definitions** Remission: HAM-D_{21} < 10	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{21}, mean (SD) rTMS: 21.86 (2.31) Sham: 18.20 (2.20)	**HAM-D_{21}** Change, mean (SD) rTMS: -10.57 Sham: -6.31 *P* = NS	**HAM-D_{21}** Response, n (%) rTMS: 4 (57) Sham: 2 (40) *P* = NR Remission, n (%) rTMS: 4 (57) Sham: 1 (20) *P* = NR

Table 17. Efficacy of rTMS versus Sham: Tier 1, MDD, augmentation strategies (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Padberg et al., 1999[73] 1 week Required failure in the current episode Fair	**rTMS (n = 6)** High frequency, 5 sessions **Low-left rTMS (n = 6)** 0.3 Hz, Left-DLPFC, 5 sessions **Sham rTMS (n = 6)** **Treatment strategy** Augmentation, 16.7% not on medication at study entry	**Mean number of failed antidepressant trials (current episode):** rTMS: 4.0 (2.2) Low-left rTMS: 3.2 (0.8) Sham: 3.2 (1.2) **Baseline Depression** HAM-D_{21}, mean (SD) High rTMS: 30.2 (9.5) Low-left rTMS: 26.7 (9.4) Sham: 22.2 (8.8)	**HAM-D_{21}** Change, mean (SD) High rTMS: -1.7 Low-left rTMS: -5.2 Sham: -1.3 *P* = NS	**HAM-D_{21}** Response: NR Remission: NR
Pallanti et al., 2010[74] 3 weeks Did not require failure in the current episode Fair	**Low plus High rTMS (n = 20)** Low then high frequency, 15 sessions **rTMS (n = 20)** Low frequency, 15 sessions Sham (n = 20) **Treatment strategy** Augmentation **Definitions** Remission HAM-D_{17} ≤ 8	**Mean number of failed antidepressant trials:** In lifetime rTMS1: 5.90 (1.48) rTMS2: 6.50 (1.48) Sham: 5.95 (1.67) **Baseline Depression** HAM-D_{17}, mean (SD) rTMS1: 28.75 (6.01) rTMS2:27.95 (5.89) Sham: 29.05 (3.54)	**HAM-D_{17}** Change, mean (SD) rTMS1: NR rTMS2:NR Sham: NR	**HAM-D_{17}** Response, n (%) rTMS1: 4 (20%) rTMS2: 7 (35%) Sham: 2 (10%) *P* = NR NNT (95% CI) rTMS1 vs Sham 10.00 (3.13 to -8.39) rTMS2 vs Sham 4.00 (2.01 to 328.11) Remission, n (%) rTMS1: 2 (10%) rTMS2: 6 (30%) Sham: 1 (5%) *P* = 0.064 NNT (95% CI) rTMS1 versus sham 20.00 (4.71 to -8.89) rTMS2 vs sham 4.00 (2.12 to 36.23)
Zheng et al., 2010[75] 4 weeks Did not require failure in the current episode Fair	**rTMS (n = 19)** High frequency, 20 sessions **Sham (n = 15)** **Treatment strategy** Augmentation – all patients taking escitalopram 2+ weeks before trial	**Mean number of failed antidepressant trials:** NR **Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 24.6 (2.9) Sham: 24.6 (2.8)	**HAM-D_{17}** Change, mean (SD) rTMS: -11.1 Sham: -1.7 *P* = NR	**HAM-D_{17}** Response, n (%) rTMS: 12 (63.2) Sham: 1 (6.7) *P* = NR Remission NR

DLPFC = dorsolateral prefrontal cortex; HAM-D_{17} = 17-Item Hamilton Depression Scale; HAM-D_{21} = 21-Item Hamilton Depression Scale; HAM-D_{25} = 25-Item Hamilton Depression Scale; Hz = hertz; n = number; NR = not reported; NS = not significant; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Another 2-week study testing augmentation compared 2 active rTMS treatments (n = 10 patients each) with each other and with 10 sessions of sham stimulation (n = 10 patients).[71] Enrolled patients were severely depressed (mean HAM-D_{21} item scores for each group between

25 and 27.3). The three groups did not appear to differ by decrease in depressive severity. However, the two active groups combined did have a greater 2-week decrease in depressive severity than the sham control group (-7.05 vs. -1.5, *P* = 0.048). Also, 2 of 10 patients in each of the active groups responded at 2 weeks, compared to no patients in the control group (*P* = NR).

A small trial compared outcomes at 2 weeks after 10 sessions of low-frequency rTMS treatment (n = 7 patients) with sham rTMS treatment (n = 5 patients).[72] The groups had moderate depressive severity (HAM-D_{21}, 21.86 for rTMS, 18.2 for control). Although mostly an augmentation study, patients were advised to discontinue benzodiazepines and mood stabilizers. ITT analyses showed that patients receiving rTMS had a 10.57 decrease in HAM-D_{21} compared to a 6.31 decrease for the sham stimulation group (*P* = NS). Response rates did not differ between the two groups (57% vs. 40%, *P* = NS). Investigators in this study also reported (57% vs. 20%, *P* = NS) the percentage of participants scoring less than 10 on the Hamilton Depression Scale. Again, small sample sizes may have limited the power to detect differences.

An additional small trial compared outcomes after 1 week of treatment with high-frequency rTMS (n = 6 patients), low-frequency rTMS to the left dorsolateral prefrontal cortex (n = 6 patients), or sham rTMS stimulation (n = 6 patients).[73] One treatment failure needed to have occurred in the current episode. Enrolled patients were moderately to severely depressed (mean HAM-D_{21} score 30.2, 26.7, and 22.2 for high-frequency, low-frequency, and control groups, respectively). Patients receiving low-frequency rTMS had a significant decrease in depressive severity relative to baseline (mean HAM-D_{21} change -1.7 for high frequency, -5.2 for low frequency to the left dorsolateral prefrontal cortex, and - 1.3 for sham stimulation), but there was no difference in treatment effect between groups in this small study.

Another 3-week augmentation trial compared bilateral high- and low-frequency rTMS (n = 20), unilateral low-frequency rTMS (n = 20), and sham rTMS stimulation (n = 20).[74] Patients in this study were severely depressed (HAM-D_{17} mean [SD] bilateral rTMS 28.75 [6.01] unilateral rTMS 27.95 [5.89] sham 29.05 [3.54]) and had a high number of previous antidepressant treatment failures (mean [SD] bilateral rTMS 5.90 [1.48] unilateral rTMS 6.50 [1.48] sham 5.95 [1.67]). In an ITT analysis, patients in the unilateral low-frequency rTMS but not the bilateral rTMS group were more likely to respond (NNT [95% CI] unilateral rTMS versus sham 4.00 [2.01-328.11] bilateral rTMS versus sham 10.00 [3.13 to -8.39]) and remit (NNT [95% CI] unilateral rTMS versus sham 4.00 [2.12-36.23]) bilateral rTMS versus sham 20.00 [4.71 to -8.89]) from treatment compared to sham stimulation.

The last augmentation study, a 4-week trial, compared high-frequency rTMS (n = 19) to sham rTMS treatment (n = 15).[75] At baseline, participants were severely depressed (HAM-D_{17} mean [SD] rTMS 24.6 [2.9] sham 24.6 [2.8]) and had been taking escitalopram for at least 2 weeks. In an ITT analysis, participants in the rTMS group had a greater decrease in depressive severity (rTMS -11.1 versus sham -1.7, *P* = NR) and a higher response rate (rTMS 63.2% sham 6.7%, *P* = 0.001).

Of the remaining three studies identified, one tested a switch strategy and two used a mixed strategy (Table 18). The single switch study tested was a small 2-week trial that compared high-frequency rTMS (n = 7 patients) to sham rTMS stimulation (n = 8 patients).[76] Patients were severely depressed (mean HAM-D_{17} for the two groups was between 20 and 23). At 2-week followup, ITT analysis indicated that the decrease in depressive severity did not differ between the two groups (-8.1 for rTMS, -5.5 for sham, *P* = NS). Similarly, the rate of response did not appear to differ (28.6% vs. 12.5%, *P* = NR).

Two studies tested a mixed strategy.[77,78] One of these trials was a good-quality 4-week study that compared 15 sessions of left-sided high-frequency rTMS (n = 35 patients) to control treatment (n = 33 patients), and was the only one to report remission rates in this tier.[77,99] Groups enrolled were in general severely depressed (mean HAM-D_{17} score 23.5). This mixed strategy was primarily a switch, although a substantial percentage of patients continued antidepressants (31% of rTMS group, 27% of control group) and benzodiazepines (26% and 24%, respectively). Outcomes were measured 1 week after completing the 4-week treatment, and all ITT analyses favored the rTMS group. Compared to controls, the rTMS group had a greater decrease in

Table 18. Efficacy of rTMS versus sham: Tier 1, MDD, mixed and switch strategies

Strategy Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Holtzheimer et al., 2004[76] 2 weeks Did not require failure in the current episode Fair	**rTMS (n = 7)** High frequency rTMS, 10 sessions **Sham rTMS (n = 8)** **Treatment strategy** Switch	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 22.7 (5.3) Sham: 20.8 (6.3)	**HAM-D_{17}** Change, mean (SD) rTMS: -8.1 Sham: -5.5 *P* = NS	**HAM-D_{17}** Response, n (%) rTMS: 2 (28.6) Sham: 1 (14.3) *P = NR*
Avery et al., 2006[77] Patients treated over 4 weeks and primary endpoint 1 week after final txt Did not require failure in the current episode Good	**rTMS (n = 35)** High frequency, 15 sessions over 4 weeks **Sham (n = 33)** **Treatment strategy** Mixed-within group differences 31% of rTMS group and 27% of control group continued taking medications **Definitions** Remission definition: HAM-D_{17} < 10	**Mean number of failed antidepressant trials:** rTMS: 3.2 (2.44) Sham: 3.3 (1.72) **Mean number of failed antidepressant trials (current episode):** rTMS: 1.46 (0.78) Sham: 1.48 (0.67) **Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 23.5 (3.9) Sham: 23.5 (2.9)	**HAM-D_{17}** Change, mean (SD) rTMS: -7.8 (7.8) Sham: -3.7 (6.3) *P* = 0.002	**HAM-D_{17}** Response, n (%) rTMS: 11 (31.4) Sham: 2 (6.1) *P* = 0.008 Remission, n rTMS: 7 (20.0) Sham: 1 (3.0) *P* = 0.033

Table 18. Efficacy of rTMS versus sham: Tier 1, MDD, mixed and switch strategies (continued)

Strategy Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Pascual-Leone et al., 1996[78] Crossover trial, 1 week Did not require failure in the current episode Fair	**rTMS (n = 17)** High frequency, 5 sessions **Sham (n = 17)** Combined data from 4 control stimulations **Treatment strategy** Mixed—within group differences and combination (All pts in both groups given 30 mg/d nimodipine)	**Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression** HAM-D_{21}, mean: NR	**HAM-D_{21}** Change, mean: TMS: NR Sham: NR *P* < 0.0005	**HAM-D_{21}** Response: NR Remission: NR

DLPFC = dorsolateral prefrontal cortex; HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{21} = 21-item Hamilton Depression Scale; HAM-D_{25} = 25-item Hamilton Depression Scale; Hz = hertz; mg/d = milligram per day; MT = motor threshold; n = number; NR = not reported; NS = not significant; *P* = p-value; pts = patients; pps = pulses per session; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt(s) = treatment(s); vs. = versus

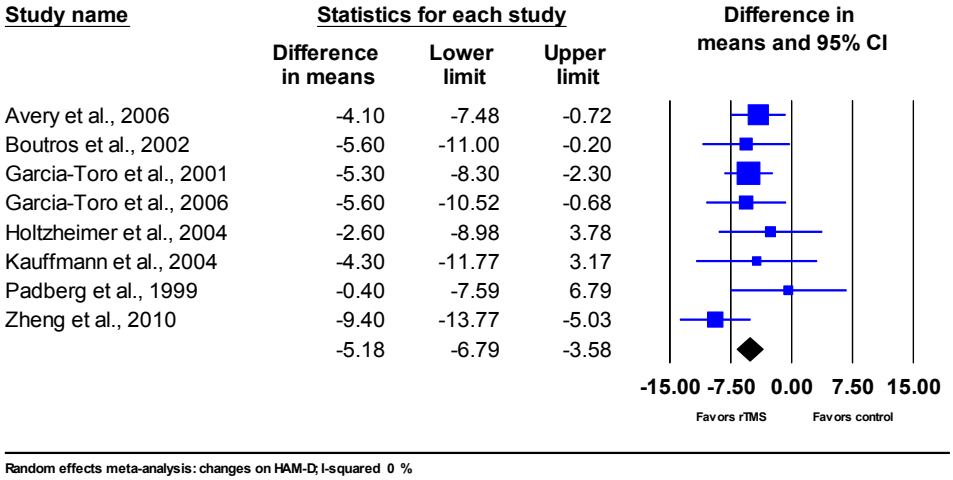
depressive severity (-7.8 vs. -3.7, *P* = 0.002), a greater response rate (31.4% vs. 6.1%, *P* = 0.008), and a greater remission rate (20.0% vs. 3.0%, *P* = 0.033).

One small mixed study used a crossover design to compare 17 TRD patients with psychotic symptoms randomized to receive different orderings of 1 high-frequency rTMS intervention and 4 different sham rTMS interventions over a 5-week period.[78] Patients had at least three episodes of depression that had been resistant to multiple medications. Baseline depressive severity was not reported. Though patients attempted to discontinue their antidepressant medication, many were unable to do so, making this strategy mixed (within group differences). All patients received nimodipine (which appears to have mood stabilizing effects) as a combination treatment with both the active rTMS and control interventions. Results suggested that the active rTMS produced greater improvement in HAM-D_{21} scores than comparison groups (*P* < 0.0005).

Meta-Analytic Synthesis of Tier 1 MDD-Only

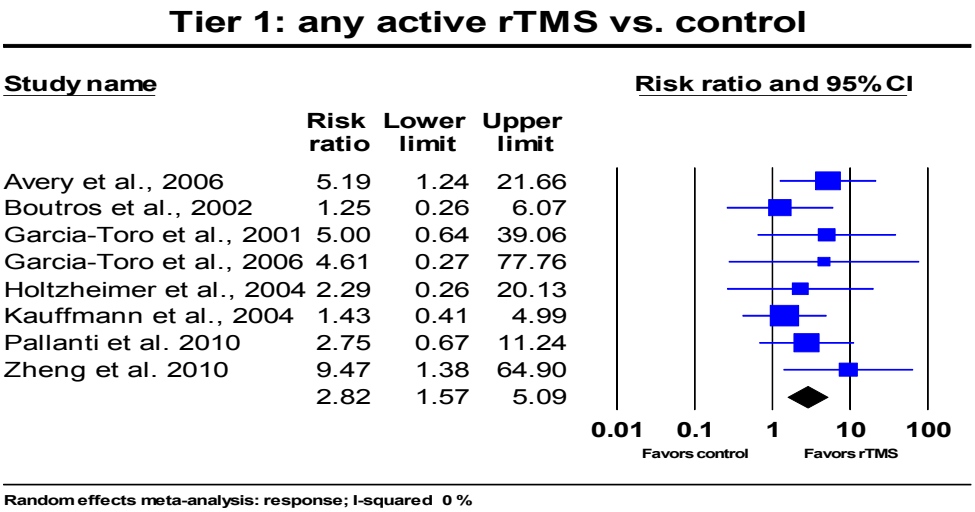
Meta-analyses supported the benefit of rTMS over sham control. The weighted mean difference in HAM-D depressive severity was -5.18 (95% CI, -6.79 to -3.58) (Figure 5).

Figure 5. Mean difference meta-analysis of changes in depressive severity comparing rTMS with sham: Tier 1, MDD



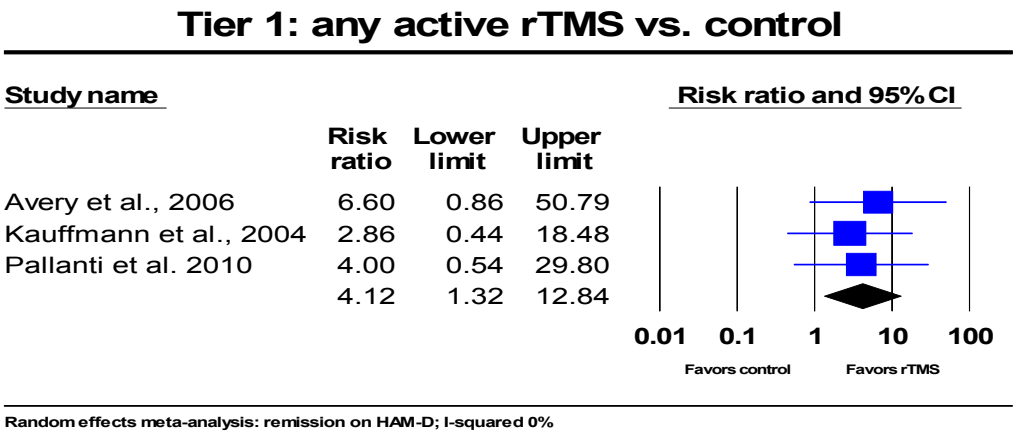
The pooled relative risk indicated that patients receiving rTMS were more than 2½ times as likely to have a treatment response as those receiving sham treatment (pooled relative risk = 2.82, 95% CI, 1.57-5.09) (Figure 6), which translates to a NNT of 5 (95% CI, 3 to 10).

Figure 6. Relative risk meta-analysis of response rates comparing rTMS with sham: Tier 1, MDD



The pooled relative risk indicated that patients receiving rTMS were more than four times as likely to achieve remission as patients receiving sham stimulation (pooled relative risk = 4.12, 95% CI, 1.32-12.84) (Figure 7). This translates to an NNT of 6 (95% CI, 4-14).

Figure 7. Relative risk meta-analysis of remission rates comparing rTMS with Sham: Tier 1, MDD



MDD/Bipolar

For rTMS versus sham, five Tier 1 studies involving MDD/bipolar mix populations, all using augmentations strategies, were identified.[18,79-82] These studies are summarized in Table 19 with detailed descriptions provided in the evidence tables (Appendix E).

Table 19. Efficacy of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder, augmentation strategies

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Bocchio-Chiavetto et al., 2008[79] Crossover, 1 week, all reported patients included in the analysis Required failure in the current episode Fair	**rTMS (n = 36)** Low Frequency rTMS (n = 18) 5 sessions OR, High Frequency rTMS (n = 18) 5 sessions **Sham (n = 15)** **Treatment strategy** Augmentation	**Diagnosis** Bipolar (%) Overall: 13.9 **Mean number of failed antidepressant trials:** Overall: 2.89 **Baseline Depression** HAM-D_{21}, mean (SD) rTMS: 23.19 (5.12) Sham: 24.53 (4.79)	**HAM-D_{21}** Change, mean (SD) rTMS: -5.69 Sham: -3.40 *P* = NR	**HAM-D_{21}** Response, n (%) NR Remission, n (%) NR
Fitzgerald et al., 2003[80] 2 weeks Did not require failure in the current episode Good	**High rTMS (n = 20)** High frequency, 10 sessions **Low rTMS (n = 20)** Low frequency, 10 sessions **Sham (n = 20)** **Treatment strategy** Augmentation **Definitions** Response1 definition: >20% decrease in MADRS score Response2 definition: ≥50% decrease in MADRS	**Diagnosis** Bipolar (%) High rTMS: 5 Low rTMS: 5 Sham: 20 **Mean number of failed antidepressant trials:** Overall: 5.68 (3.40) **Baseline Depression** MADRS, mean (SD) High rTMS: 36.05 (7.55) Low rTMS G2: 37.70 (8.36) Sham: 35.75 (8.14)	**MADRS** Change, mean (SD) High rTMS: -5.25 Low rTMS G2: -5.5 Sham: -0.35 High rTMS versus sham, low rTMS versus sham, *P* < 0.005	**MADRS** Response1, n (%) High rTMS: 8 (40) Low rTMS: 7 (35) Sham: 2 (10) *P* = 0.07 Response2, n (%) High rTMS: 0 (0) Low rTMS: 1 (5) Sham: 0 (0) *P* = NR

Table 19. Efficacy of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder, augmentation strategies (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Fitzgerald et al., 2006[18] 6 weeks of txt (after 2 weeks, patients with < 20% decrease in score exited with LOCF) Did not require failure in current episode **Good**	**High plus Low rTMS (n = 25)** High frequency rTMS up to 30 sessions plus low frequency rTMS up to 30 sessions **Sham (n = 25)** **Treatment strategy** Augmentation, 23% not taking any medication at start of study **Definitions** **Remission definition: HAM-D_{17} < 8**	**Diagnosis** Bipolar (%) rTMS: 16 Sham: 16 **Mean number of failed antidepressant trials:** rTMS: 5.6 (3.1) Sham: 6.2 (3.0) **Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 22.5 (7.4) **Sham: 19.8 (4.4)**	**HAM-D_{17}** rTMS: -10.2 Sham: 1.1 *P* < 0.001	**HAM-D_{17}** Response, n (%) rTMS: 13 (52) Sham: 2 (8) *P* = 0.001 Remission (%) rTMS: 10 (40) Sham: 0 (0) ***P* = 0.001**
Su et al., 2005[81] 2 weeks, completers analysis Did not require failure in the current episode Fair	**20 Hz rTMS (n = 11)** High frequency (20 Hz), 10 sessions **5 Hz rTMS (n = 11)** High frequency (5 Hz),10 sessions **Sham (n = 11)** **Treatment strategy** Augmentation **Definitions** Remission defined as HAM-D_{21} < 8	**Diagnosis** Bipolar (%) 20 Hz rTMS: 10 5 Hz rTMS G2: 20 Sham G3: 20 **Mean number of failed antidepressant trials:** 20 Hz rTMS: NR 5 Hz rTMS G2: NR Sham G3: NR **Baseline Depression** HAM-D_{21}, mean (SD) 20 Hz rTMS: 23.2 (7.5) 5 Hz rTMS: 26.5 (5.2) Sham: 22.7 (4.7)	**HAM-D_{21}*** Change, mean (SD) 20 Hz rTMS: -13.4 (4.9) 5 Hz rTMS: -14.2 (6.0) Sham: -3.7 (9.3) *P* < 0.01 *n analyzed: n = 10 in each group	**HAM-D_{21}*** Response, n (%) 20 Hz rTMS: 6 (60) 5 Hz rTMS: 6 (60) Sham: 1 (10) *P* = 0.01 Remission, n (%) 20 Hz rTMS: 5 (50) 5 Hz rTMS: 5 (50) Sham: 0 (0) *P* = NR
Triggs et al., 2010[82] 2 weeks Did not require failure in the current episode Fair	**High rTMS (n = 18)** High frequency, 10 sessions **High right rTMS (n = 16)** High frequency to the right prefrontal cortex, 10 sessions **Sham left (n = 7)** **Sham right (n = 7)** **Treatment strategy** Augmentation NOTE: Patients in all groups also received a social support intervention	**Baseline Depression** HAM-D_{24}, mean (SD) rTMS1: 28.2 (6.0) rTMS2: 27.2 (4.8) Sham1: 27.7(3.5) Sham2: 27.3 (2.7) **Diagnosis** Bipolar (%) rTMS1: 0 rTMS1: 12.5 Sham1: 0 Sham2: 0 **Mean failed antidepressant trials** NR	**HAM-D_{24}** Change, mean (SD) rTMS1: -8.4 rTMS2: -13.5 Sham1: -5.7 Sham2: -13.9 *P* = 0.14	**HAM-D_{24}** Response, n (%) rTMS1: 4 (22.2%) rTMS2: 5 (31.3%) Sham1: 2 (28.6%) Sham2: 4 (57.1%) *P* = NR Remission: NR

HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{21} = 21-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; n = number; NR = not reported; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt = treatment

One fair-quality trial compared 1 week of low-frequency rTMS (a group of 36, consisting of 18 who received low-frequency rTMS and 18 who received high-frequency rTMS) with 1 week of sham rTMS stimulation (involving a subgroup of 15 patients from the above group of 36 who received control treatment 8 weeks after having received rTMS).[79] Patients entered treatment severely depressed (mean HAM-D_{21} severity 23.19 in rTMS group, 24.53 in sham group). No difference in decrease in HAM-D_{21} item severity was identified (-5.69 in active group, -3.40 in control group, *P* = not reported).

One good-quality trial compared three groups: one with high-frequency rTMS (n = 20 patients), one with low-frequency rTMS (n = 20 patients), and one with sham stimulation (n = 20 patients) following 2 weeks of treatment.[80] The three groups had MADRS scores averaging between 35 and 38, consistent with severe depression. Both the high-frequency and low-frequency groups had 5 percent bipolar patients, and the control group had 20 percent. An ITT analysis favored the two rTMS groups. Both the high-frequency (-5.25) and low-frequency (-5.5) groups had greater decrease in MADRS severity than the sham group (-0.35, $P < 0.005$ for each comparison with control). Using a definition of response as > 20 percent improvement in MADRS score, the two active groups tended to have greater rates of response (40% and 35%, respectively) compared to the sham stimulation group (10%) ($P = 0.07$ for both comparisons). Using the more standard definition of response as a 50 percent decrease, only one patient (in the low frequency group) responded by study end.

Another good-quality, 6-week study compared high-frequency rTMS plus low-frequency rTMS (n = 25 patients) to sham rTMS stimulation (n = 25 patients).[18] Failure was not required in the current episode. The number of treatments depended on the presence of at least partial response. Patients entering the rTMS were severely depressed (mean HAM-D_{17} of 22.5), while the control group was only moderately depressed (mean HAM-D_{17} of 19.8). Sixteen percent of each group had bipolar disorder. rTMS patients had better outcomes than patients receiving sham stimulation on each response measure. Compared to control, rTMS patients had a greater improvement in HAM-D scores (-10.2 vs. -1.1, $P < 0.001$), greater response rate (52% vs. 8%, $P = 0.001$), and a greater remission rate (40% vs. 0%, $P = 0.001$).

A 2-week study compared three groups: those receiving high-frequency rTMS (20 hertz [Hz]) (n = 11 patients), those receiving "lower" high-frequency rTMS (5 Hz) (n = 11 patients), and those receiving sham rTMS treatment (n = 10 patients).[81] Patients entering the study were severely depressed (mean HAM-D_{21} severity for 20 Hz group 23.2, 5 Hz group 26.5, and sham group 22.7) The 20 Hz high-frequency group had 10 percent bipolar patients, and the other two group each had 20 percent with a bipolar depression. A treatment completer analysis showed that patients in the active groups had a greater decrease in HAM-D_{21} severity (-13.4 and -14.2, respectively) than the control group (-3.7, $P < 0.01$ for each comparison). Similarly, response favored the two rTMS groups (60% for each vs. 10% for the sham stimulations comparison, $P = 0.01$ for both). Finally, both rTMS treatments had greater remission rates (50%) than the sham control group, which had no remitters (*P* = not reported).

A fifth augmentation study compared high-frequency rTMS to the left dorsolateral prefrontal cortex (n = 18) and high-frequency rTMS to the right dorsolateral prefrontal cortex (n = 16), with sham rTMS treatments to the same locations (left n = 7, right n = 7).[82] Unlike other studies comparing rTMS and sham stimulation, in this study all patients also received a social support intervention. At baseline, patients were severely depressed (HAM-D_{24} mean [SD] high rTMS 28.2 [6.0], high right rTMS 27.2 [4.8], sham left 27.7 [3.5], sham right 27.3 [2.7]), and only two patients in the high right rTMS group had bipolar disease (high right rTMS 12.5%, all other

groups 0%). Patients in all groups had a decrease in depressive severity ($HAM\text{-}D_{24}$ mean high rTMS -8.4, high right rTMS -13.5, sham left -5.7, sham right -13.9, *P* = NR), but patients in the active rTMS groups were not more likely to respond to treatment compared to those in the sham group (high rTMS 22.2%, high right rTMS 31.3%, sham left 28.6%, sham right 57.1%, *P* = 0.14). It is possible that the inclusion of a social support intervention may have muffled the effects of rTMS in this study.

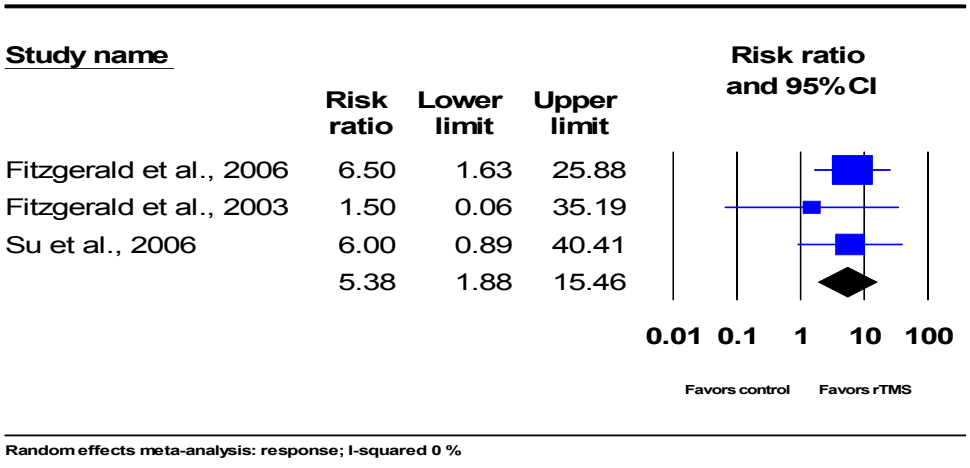
Meta-Analytic Synthesis of Tier 1 MDD/Bipolar mix Outcomes

We were able to quantitatively synthesize outcomes from four of the five studies within an MDD/bipolar mix Tier 1 population.[18,79-82] The fifth study, an outlier, was excluded from the analysis.[82] Though the rTMS intervention in this study used similar stimulation parameters to others in this category, an extensive supportive social intervention distinguished it from the other trials. This additional co-intervention may have diminished the comparative efficacy of rTMS and sham stimulation. Based on these concerns and the heterogeneity introduced when this study was included, we excluded this study from the meta-analyses.

For changes in depressive severity involving the three studies using HAM-D as an outcome, patients receiving rTMS on average had approximately a 7-point greater decrease relative to sham control (-7.25, 95% CI, -10.87 to -3.64). Because sample sizes were small and responses to placebo varied in the small control groups, the heterogeneity was high (I^2 = 90%) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

The pooled relative risk (HAM-D or MADRS) indicated that patients receiving rTMS were more than five times as likely to have a treatment response as those receiving sham treatment (5.38, 95% CI, 1.88-15.46) (Figure 8), which translates to an NNT of 3 (95% CI, 1-14).

Figure 8. Relative risk meta-analysis of response rates comparing rTMS versus sham: Tier 1, MDD/≤ 20 percent bipolar disorder



We were unable to quantitatively synthesize remission rates because only two studies in this population reported this outcome; both studies indicated greater absolute remission rates for rTMS compared with sham.[18,81]

Tier 1 MDD and MDD/Bipolar Combined

Meta-analyses combining TRD studies (Tier 1) from both MDD and MDD/bipolar mix populations continued to support the benefit of rTMS over sham control. The mean difference in HAM-D depressive severity was -5.74 (95% CI, -7.79 to -3.68) (Figure 9). The pooled relative risk indicated that patients receiving rTMS were more than three times as likely to respond as those receiving placebo (pooled relative risk 3.34, 95% CI, 1.92 to 5.82) (Figure 10), which translates into a NNT of 5 (95% CI, 3-10). Remission rates also favored rTMS. The pooled relative risk for remission was 6.12 (95% CI, 1.89 to 19.80), which translates to a NNT of 4 (95% CI, 2-20) (Figure 11).

MDD/bipolar mix point estimates tended to be slightly higher than those for MDD-only, but confidence intervals overlapped, suggesting no clear difference. Indeed, combining the two populations did not affect the direction nor did it substantially impact the magnitude of the results, and the combined results were consistent with what was reported for the Tier 1 syntheses separately.

Figure 9. Mean difference meta-analysis of changes in depressive severity comparing rTMS versus sham: Tier 1

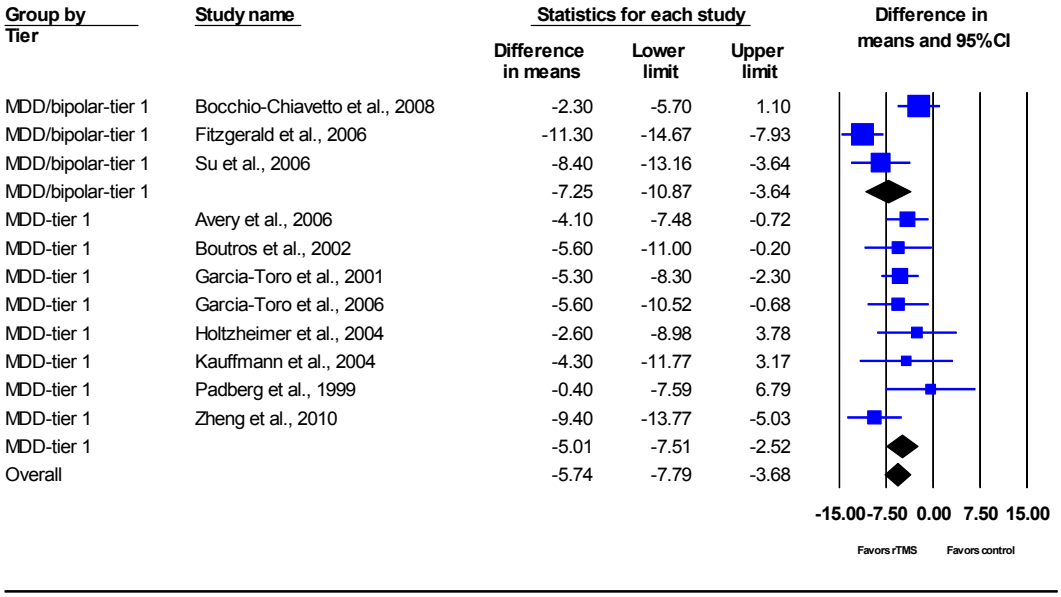


Figure 10. Relative risk meta-analysis of response rates comparing rTMS versus sham: Tier 1

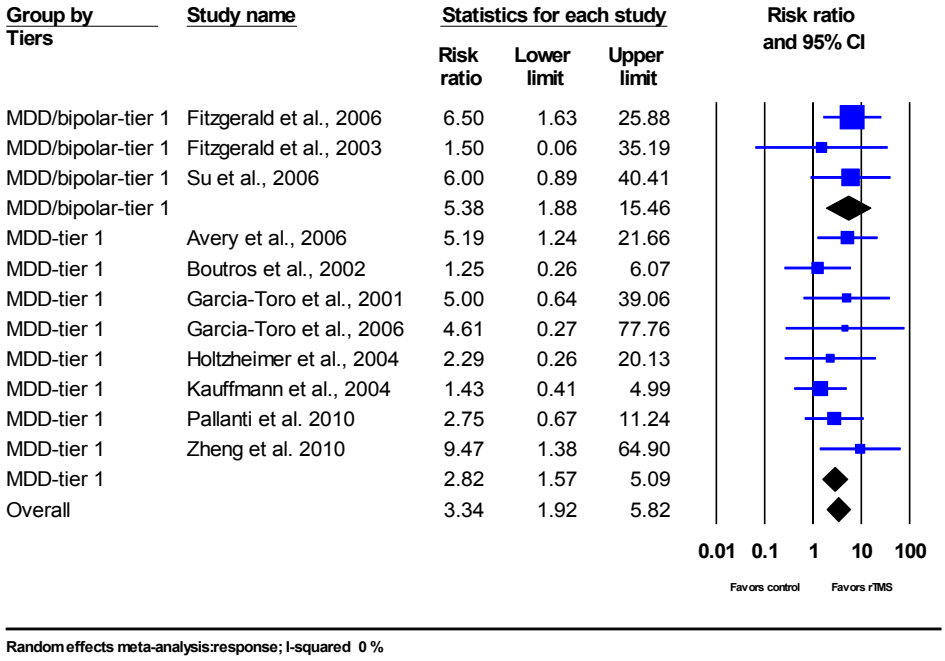
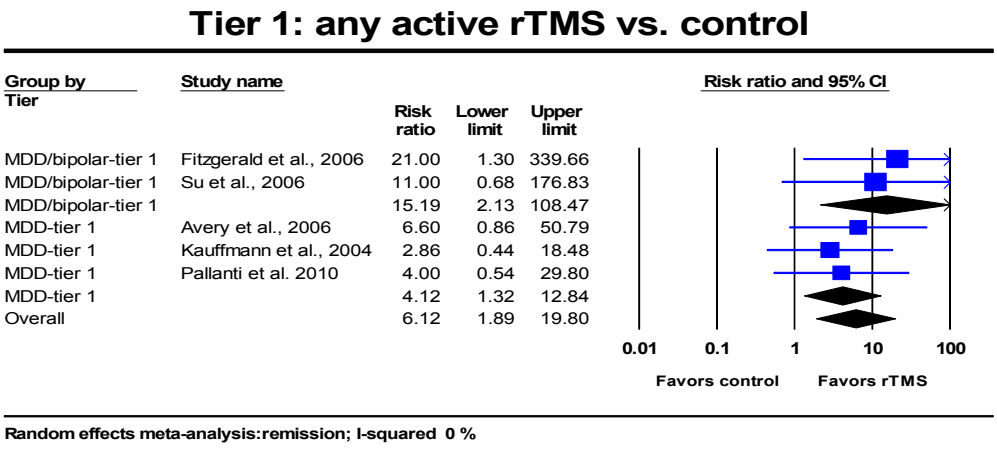


Figure 11. Relative risk meta-analysis of remission rates comparing rTMS versus sham: Tier 1



Tier 2: Patients With one or More Treatment Failures

Consideration of Tier 2 provided six additional studies: four MDD-only studies (reported in six articles)[83-87] and two additional MDD/bipolar mix studies.[88,89]

MDD-Only

Consideration of Tier 2 study populations added four additional studies reported in five articles.[83-87] Two trials were rated good quality, while two were rated fair quality. All employed switch strategies, and evaluated rTMS versus sham stimulation in patients with one or more treatment failures (Table 20).

A large study, rated to be of good quality, compared up to 6 weeks of high frequency (n = 93) with sham rTMS stimulation (n = 98).[83] On average, patients in the trial had moderate to severe depression (mean HAM-D_{24} rTMS 26.3 sham 26.5) and had three antidepressant failures

in their lifetime (rTMS 3.34 sham 3.28). Using a modified ITT analysis, patients in the rTMS group had a greater decrease in depressive severity (at week 3, rTMS -4.7 sham -3.3, $P = 0.06$) and higher rates of response (OR, 4.6 [95% CI, 1.47-14.42]) and remission (OR, 4.18 [95% CI, 1.32-13.24].

A brief 1-week trial compared high-frequency rTMS (n = 10 patients) to sham stimulation (n = 10 patients).[84,85] Enrolled patients had moderate to severe depression (mean HAM-D severity approximately 23 in each group). Whether the analysis conducted was ITT or treatment completer was not clear. Results demonstrated no difference between the rTMS and sham groups in the decrease of depressive severity (-9 vs. -6.5, $P > 0.66$), the rate of response (30% in each), or the rate of remission (20% in each).

The largest trial the second good-was a 4-week study comparing high-frequency rTMS (n = 165 patients) to sham stimulation (n = 160 patients).[87] Patients were required to have at least one but not more than four failed adequate antidepressant treatments in this or the most recent episode or to have failed to tolerate four adequate lifetime medication trials. The groups participating were severely depressed (mean HAM-D_{17} approximately 23). A modified ITT analysis involving 301 patients at 6 weeks favored rTMS, which showed a greater decrease in depressive severity (mean HAM-D_{17} decrease of 5.5 versus 3.3, $P = 0.005$) and a greater response rate (24.5% vs. 13.7%, $P < 0.05$), while there was a trend toward greater remission rates with rTMS (15.5% vs. 8.9%, $P = 0.065$).

The fifth trial compared 2 weeks of rTMS stimulation among four groups: high-frequency rTMS (n = 10 patients), low frequency left-sided rTMS (n = 10 patients), low frequency right-sided rTMS (n = 10 patients), and sham control (n = 15 patients).[86] All patients had been referred for ECT following treatment failure of an adequate course of an antidepressant medication. The groups involved were severely depressed (mean HAM-D_{21} item ranged between 27 and 28 for each group). It was unclear whether the analysis conducted was ITT or treatment completers. For each outcome, the high-frequency rTMS and the low-frequency rTMS groups appeared to produce better outcomes than the low frequency left-sided rTMS and sham groups. The high left-sided rTMS and low right-sided rTMS groups produced a greater decrease in depressive severity than the low left rTMS or sham group (mean change in HAM-D_{21} high rTMS > low left rTMS + sham and low right rTMS > low left rTMS + sham, $P < 0.0005$). Response rates (50% and 50% vs. 0% and 0%, P = not reported) and remission rates (30% and 10% vs. 0% and 0%; P = not reported) also appeared higher in the same two groups.

Table 20. Efficacy of rTMS versus sham: Tier 2, MDD

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
George et al., 2010[83] Up to 6 weeks, mITT Did not require failure in the current episode Good	**rTMS (n = 92*)** High frequency, 15 sessions **Sham (n = 98*)** *mITT (N randomized = 199) **Treatment strategy** Switch **Definitions** Remission definition HAM-D_{24} < 10 at two consecutive visits	**Mean failed antidepressant trials:** Current/lifetime rTMS: 1.62/3.34 Sham: 1.41/3.28 **Baseline Depression** HAM-D_{24}, mean (SD) rTMS: 26.3 (5.0) Sham: 26.5 (4.8)	**HAM-D_{24}** At 3 weeks Change**, mean (SD) rTMS: -4.7 Sham: -3.1 **observed rTMS n = 83 Sham n = 91 95% CI effect estimate (adjusted) -4.23 to 0.10, *P* = 0.06	**HAM-D_{24}** Response*, n (%) rTMS: 14 (15.2) Sham: 5 (5.1) OR, 4.6 (95% CI, 1.47-14.42) Remission*, n (%) rTMS: 13 (14.1) Sham: 5 (5.1) OR, 4.18 (95% CI, 1.32-13.24)
Manes et al., 2001[84] and Moser et al., 2002[85] 1 week, all reported patients included in analysis Did not require failure in the current episode Fair	**rTMS (n = 10)** High frequency, 5 sessions **Sham (n = 10)** **Treatment strategy** Switch **Definitions** Response definition: 50% reduction in HAM-D and no longer met DSM criteria for major or minor depression Remission definition: HAM-D < 8	**Diagnosis** Major Depression,% rTMS: 80 Sham: 100 Dysthymia,% rTMS: 20 Sham: 0 **Mean number of failed antidepressant trials:** rTMS: 4 (2.3) Sham: 4 (1.2) **Baseline Depression** HAM-D NR, mean (SD) rTMS: 22.7 (5.2) Sham: 22.7 (7.1)	**HAM-D NR** Change, mean (SD) rTMS: -9 Sham: -6.5 *P* >0.66	**HAM-D NR** Response, n (%) rTMS: 3 (30) Sham: 3 (30) *P* = NS Remission, n (%) rTMS: 2 (20) Sham: 2 (20) *P* = NR
Stern et al., 2007[86] 2 weeks, all reported patients included in analysis Required failure in the current episode Fair	**rTMS -1(n = 10)** High frequency,10 sessions **rTMS -2(n = 10)** Low frequency (1 Hz), Left-DLPFC, 10 sessions **rTMS-3 (n = 10)** Low frequency, 10 sessions **Sham (n = 15)** **Treatment strategy** Switch **Definitions** Remission definition HAM-D_{21} ≤ 10	**Mean number of failed antidepressant trials:** rTMS-1: NR rTMS-2: NR rTMS-3: NR **Baseline Depression** HAM-D_{21}, mean (SD) rTMS-1: 27.8 (3.2) rTMS-2: 27.6 (3.9) rTMS-3: 27.9 (3.8) Sham: 27.4 (2.9)	**HAM-D_{21}** Change, mean (SD) rTMS-1: -12.7 rTMS-2: 0.0 rTMS-3: -12.1 Sham: -0.7 rTMS-1 > rTMS-2 + sham and rTMS > rTMS-2 + sham, P < 0.0005	**HAM-D_{21}** Response, n (%) rTMS-1: 5 (50) rTMS-2: 0 (0) rTMS-3: 5 (50) Sham: 0 (0) *P* = NR Remission, n (%) rTMS-1: 3 (30) rTMS -2: 0 (0) rTMS -3: 1 (10) Sham: 0 (0) *P* = NR

Table 20. Efficacy of rTMS versus sham: Tier 2, MDD (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
O'Reardon, 2007[87] 6 weeks; at week 4, patients not responding left study with LOCF, mITT Did not require failure in the current episode Good	**rTMS (n = 165)** High frequency, up to 30 sessions **Sham (n = 160)** **Treatment strategy** Switch **Definitions** Remission definition: HAM-D_{17} ≤ 7	**Mean number of failed antidepressant trials:** rTMS: 1.6 Sham: 1.6 **Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 22.6 (3.3) Sham: 22.9 (3.5)	**HAM-D_{17}*** Change, mean (SD) rTMS:-5.5 Sham:-3.3 *P* = 0.005 *Results based on rTMS: n = 155 Sham: n = 146	**HAM-D_{17}*** Response, n (%) rTMS: 38 (24.5) Sham: 20 (13.7) *P* < 0.05 Remission, n (%) rTMS: 24 (15.5) Sham: 13 (8.9) *P* = 0.065

DLPFC = dorsolateral prefrontal cortex; DSM = Diagnostic and Statistical Manual; HAM-D = Hamilton Depression Scale; HAM-D_{21} = 21-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; mITT = modified intention to treat; n = number; NR = not reported; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar

Consideration of Tier 2 added two MDD/bipolar mix studies. The first was a 2-week switch study comparing high-frequency rTMS (n = 10 patients) to sham rTMS treatment (n = 10 patients).[88] This study is summarized in Table 21, with a detailed description provided in the evidence tables (Appendix E). All patients had at least one treatment failure following an adequate antidepressant trial during the current episode except one, who had previously received ECT and had proven treatment resistant to antidepressants in the past). Patients entered into the study with a severe degree of depression (approximately 37 on the HAM-D_{25} item scale in each group). As with the Tier 1 group, the rTMS group had a mean HAM-D_{25} decrease of 14 compared to a decrease of 0.2 in the control group ($P < 0.01$). Response rates also favored rTMS (10% vs. 0%, $P = 0.09$).

Over a duration of 3 weeks, the second study compared the combination of high-frequency rTMS plus escitalopram (n = 25 patients) with sham rTMS plus escitalopram (n = 24 patients) in patients who had discontinued their previous antidepressant pharmacotherapy (failed within the current episode).[89] Those participating were moderately to severely depressed (mean HAM-D_{17} was 25.3 [SD 3.0] in rTMS group and 24.7 [SD 3.2] in the sham control). Authors conducted a modified ITT analysis. Mean depressive severity change was -8.9 in the rTMS escitalopram group and -5.6 in the sham alone group. This comparison favored rTMS plus pharmacotherapy over pharmacotherapy alone with the authors reporting an effect size of 0.78 (95% CI, 0.18 to 1.39).

Table 21. Efficacy of rTMS versus sham: Tier 2 MDD and ≤ 20 percent bipolar disorder

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
Berman et al., 2000[88] 2 weeks Did not require failure in the current episode Fair	**rTMS (n = 10)** High frequency, 10 sessions **Sham (n = 10)** **Treatment strategy** Switch	**Diagnosis** Bipolar (%) rTMS: 0 Sham: 10 **Mean number of failed antidepressant trials:** rTMS: 5 Sham: 3.5 (plus 1 failed augmentation medication each) **Baseline Depression** HAM-D_{25}, mean rTMS: 37.1 Sham: 37.3	**HAM-D_{25}** Change, mean* (SEM) rTMS: -14.0 (3.7) Sham: -0.2 (4.1) *P* < 0.01 *adjusted mean decreases based on best fit slopes	**HAM-D_{25}** Response, n (%) rTMS: 1 (10) Sham: 0 (0) *P* = 0.09
Bretlau et al., 2008[89] 3 weeks, mITT Required failure in the current episode. Fair	**rTMS (n = 25)** High frequency, 15 sessions over 3 weeks **Sham (n = 24)** 20 mg escitalopram **Treatment Strategy** Combination all patients received 20 mg escitalopram	**Previous manic episodes:** rTMS: 4.5% Sham: 13.0% **Mean number of failed antidepressant trials (current episode):** rTMS: 2.8 (0.9) Sham: 2.5 (0.9) **Baseline Depression:** HAM-D_{17}, mean* (SD) rTMS: 25.3 (3.0) Sham: 24.7 (3.2) *based on rTMS: n = 22 Sham: n = 23	**HAM-D_{17}** Change, mean* (SD) rTMS: -8.9 Sham: -5.6 Effect size: 0.78 (0.18-1.39)*	**HAM-D_{17}** Response, n (%) NR Remission, n (%) NR

HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{25} = 25-item Hamilton Depression Scale; mITT = modified intention to treat; n = number; rTMS = repetitive transcranial magnetic stimulation; SEM = standard error of measurements

Tier 3: Patients With Probable TRD

Three trials comparing rTMS with sham stimulation were identified in Tier 3 (Table 22).

MDD-Only

There were no eligible studies.

MDD/Bipolar

Three small studies compared rTMS versus a sham control; these studies are summarized in Table 22 and described in detail in the evidence tables (Appendix E). Two studies reported significantly better outcomes for rTMS and the third identified a trend in this direction. Results did not vary by strategy. Study duration did not appear to affect outcomes.

Table 22. Efficacy of rTMS versus sham: Tier 3 MDD and ≤ 20 percent bipolar disorder

Author, year Study Design Primary endpoint(s) Quality Tier	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Bortolomasi et al., 2006[90] 1 week, all reported patients included in analysis Did not require failure in the current episode Tier 3—"drug resistance" not defined Fair	**rTMS (n = 12)** High frequency, 5 sessions **Sham (n = 7)** **Treatment strategy** Augmentation	**Diagnosis** Bipolar (%) rTMS: 16.7 Sham: 14.3 **Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression:** HAM-D_{24} rTMS: 25.17 Sham: NR	**HAM-D_{24}** Change, mean (SD) rTMS: -13.84 Sham: NR *P* = data NR but text states not significant	**HAM-D_{24}** Response, n (%) NR Remission, n (%) NR
George et al., 1997[91] Crossover, 2 weeks Tier 3—all patients had 1+ implied current episode failures Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 12)** **Treatment strategy** Mixed-within group difference Patients discontinued their (failed) ADs with the exception of 3 patients who were partial responders	**Diagnosis** Bipolar (%) Overall: 8.3 **Mean number of failed antidepressant trials:** Overall: 13.4 **Baseline Depression:** HAM-D_{21} Overall: 28.5 (4.2)	**HAM-D_{21}** Change, mean (SD) rTMS: -5.25 Sham: +3.33 *P* < 0.03	**HAM-D_{21}** Response, n (%) NR Remission, n (%) NR

Table 22. Efficacy of rTMS versus sham: Tier 3 MDD and ≤ 20 percent bipolar disorder (continued)

Author, year Study Design Primary endpoint(s) Quality Tier	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Moller, 2006[92] Crossover, within 1 week of completing 1 week of txt Did not require failure in the current episode. Tier 3—TRD not defined Fair	**rTMS (n = 10)** High frequency, 5 sessions **Sham (n = 10)** **Treatment strategy** Augmentation	**Diagnosis** Bipolar (%) Overall: 20 **Mean number of failed antidepressant trials:** rTMS: NR Sham: NR **Baseline Depression:** HAM-D_{17} Median (range) rTMS: 20 (13-37) Sham: 16 (7-31)	**HAM-D_{17}** Change (median) rTMS: -7 Sham: -1 *P* = 0.075	**HAM-D_{17}** Response, n (%) NR Remission, n (%) NR

Ads = antidepressants; ; HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{21} = 21-item Hamilton Depression Scale; HAM-D_{24} = 24-item Hamilton Depression Scale; n = number; NR = not reported; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TRD = treatment-resistant depression; txt = treatment

With the exception of a control arm in one study, all groups were severely depressed. All studies used high-frequency rTMS and none required treatment failure in the current episode.

One study compared 5 sessions per week of high-frequency rTMS (n = 12 patients) to sham stimulation (n = 7 patients).[90] The authors indicated that patients needed to meet criteria for "drug resistance," but this definition was not provided. Patients enrolled were depressed (mean HAM-D_{24} for rTMS group = 25.17). Those receiving rTMS had a greater decrease in mean HAM-D_{24} severity than those in the control group (the text states that the difference is statistically significant, but it does not report the test).

The other augmentation trial was a small randomized crossover study that compared patients (n = 10) receiving 1 week of high-frequency versus sham stimulation.[100] Patients were referred to the study because their depression was "drug resistant," and the authors note that "various antidepressants had previously been tried without adequate success." On average, patients entering the study were moderately to severely depressed (median HAM-D_{17} for sham = 16 [moderate] and for rTMS = 20 [severe]). Outcomes suggested benefit for rTMS as measured by mean change in depressive severity (-7 vs. -1), but in this small sample this difference was insignificant (*P* = 0.075).

A third trial tested a mixed strategy that also used a crossover design. The study (n = 12 patients) compared 2-week outcomes for patients who received, in randomized order, 2 weeks of high-frequency rTMS and 2 weeks of sham rTMS stimulation.[91] All patients still met criteria for a major depressive episode despite treatment with an antidepressant, suggesting failure in the current episode. Patients entering the trial were severely depressed (mean HAM-D_{21} score = 28.5). Results from an ITT analysis favored active treatment; the rTMS group had a greater mean change in depressive severity (-5.25 vs. + 3.33, $P < 0.03$).

Tiers 1-3 Combined

Twenty-four studies comparing rTMS with sham rTMS stimulation were identified.[18,69-82,84-88,90,91] The majority of studies for this comparison found that rTMS resulted in significantly greater efficacy as measured by change in depressive severity, response, and remission. Other studies did not report tests of statistical significance or were underpowered to detect differences between groups. Differences in efficacy by tier and inclusion of patients with bipolar disorder were assessed via stratified meta-analyses.

Meta-Analytic Synthesis of Outcome in an MDD-Only Population (Tiers 1, 2, and 3 Combined)

Meta-analyses combining studies from only Tier 1 and Tier 2 studies (as there were no Tier 3 studies identified) supported the benefit of rTMS over sham control and were consistent with Tier 1 analyses. The weighted mean difference in HAM-D depressive severity was -4.40 (95% CI, -6.04 to -2.76) (Figure 12). The pooled relative risk indicated that patients receiving rTMS were approximately twice as likely to respond as those receiving placebo (pooled relative risk 2.18, 95% CI, 1.47 to 3.22) (Figure 13), which translates into a NNT of 6 (95% CI, 4—10). Pooled relative risk for remission rates only slightly favored rTMS at 2.37 (95% CI, 1.20 to 4.69) (Figure 14).

Combining these three tiers for MDD-only populations provided a more conservative point estimate and a narrower confidence interval for each of the three outcomes than the quantitative syntheses for Tier 1 MDD-only.

Figure 12. Mean difference meta-analysis of changes in depressive severity comparing rTMS with sham: Tiers 1 & 2, MDD

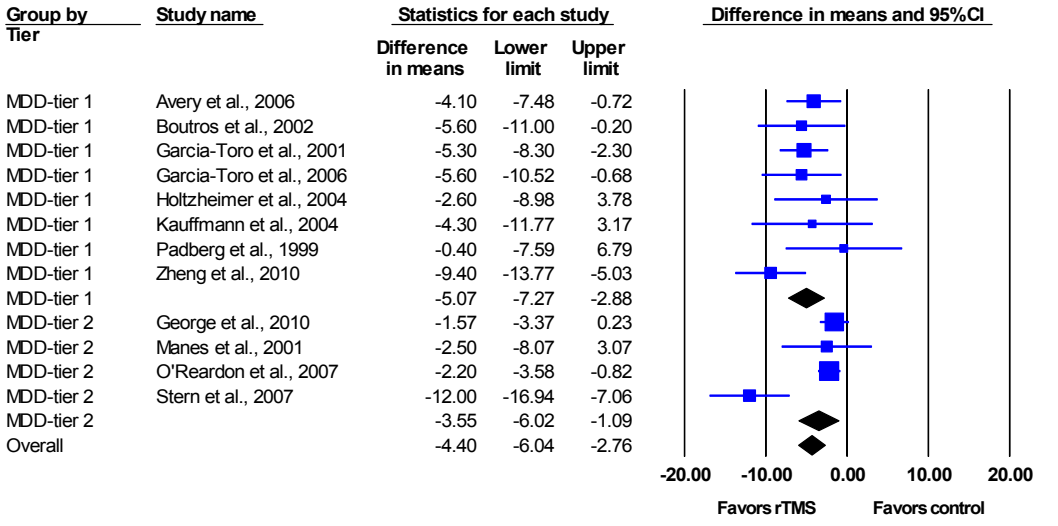


Figure 13. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, MDD

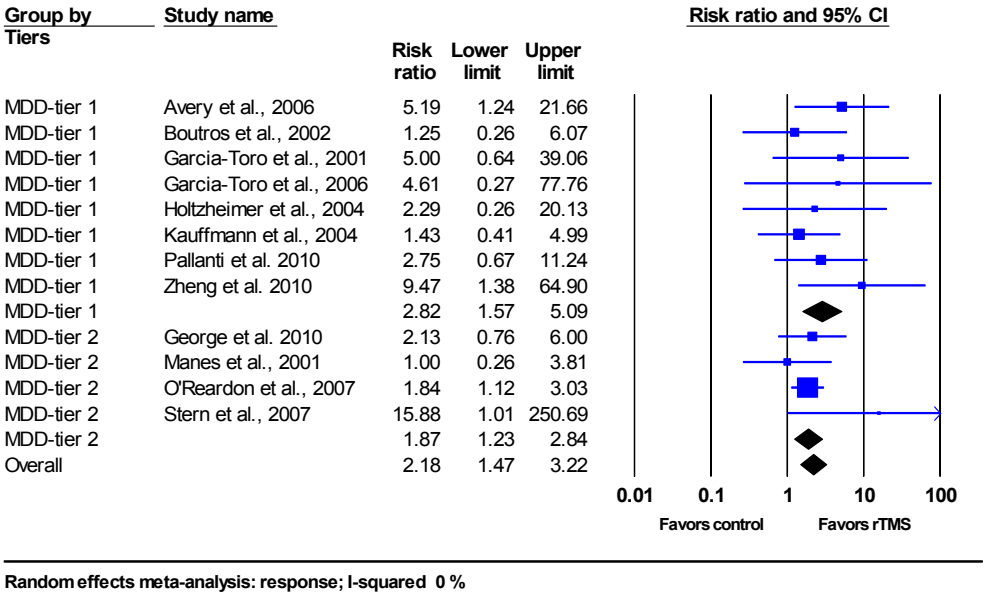
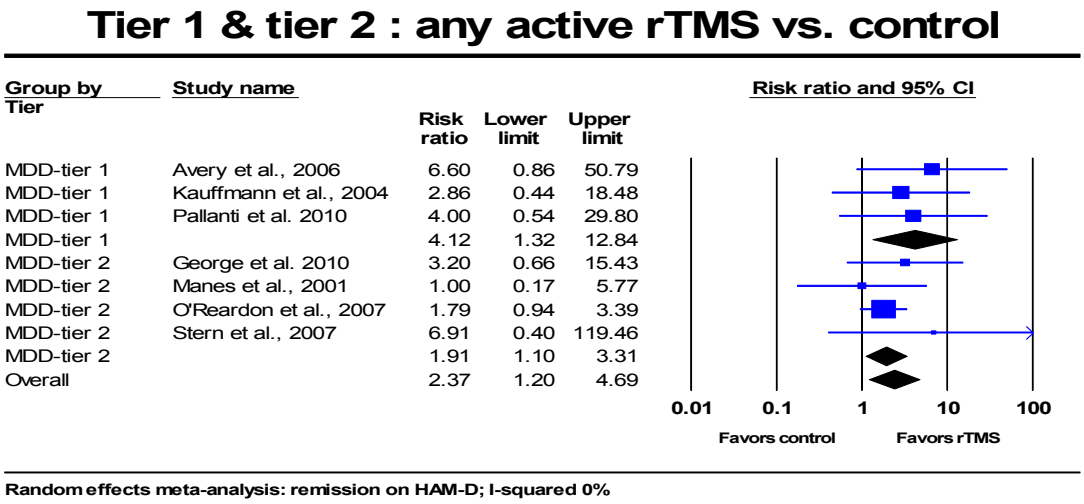


Figure 14. Relative risk meta-analysis of remission rates comparing rTMS with sham: Tiers 1 & 2, MDD



Meta-Analytic Synthesis of MDD/Bipolar mix Outcomes (Tiers 1, 2, and 3 Combined)

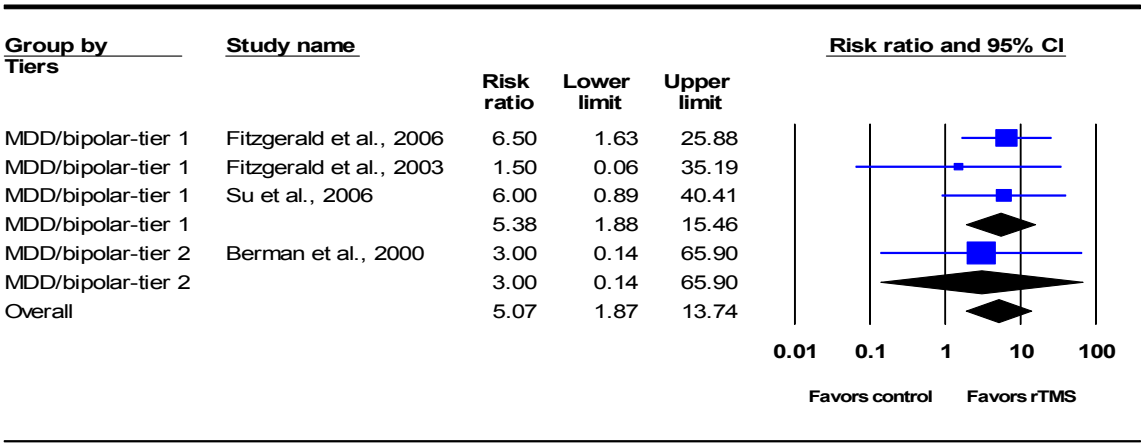
Meta-analyses combining studies from all tiers in this population allowed for comparisons of response and remission in Tier 1 and Tier 2 studies and for change in depressive severity within all three tiers. Combining this data with Tier 1 results continued to support benefit for rTMS. For changes in depressive severity as measured by the mean HAM-D difference, patients receiving rTMS on average had a decrease of nearly 8 points relative to sham control (-7.73, 95% CI, -13.31 to -2.14). Because sample sizes were small and responses to placebo varied in the small control groups, the heterogeneity was high (I^2 = 90%) and our estimates are uncertain with

respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

Response rates also favored rTMS, with rTMS groups being more than five times as likely to achieve response (random effects relative risk 5.07, 95% CI, 1.87 to 13.74) (Figure 15), leading to a NNT of 3 (95% CI, 1-14). We were unable to quantitatively synthesize remission results due to the small number of studies reporting this outcome.

Compared to the meta-analytic synthesis of Tier 1 MDD/bipolar mix studies, the combination of Tiers 1–3 produced nearly identical point estimates for change in depressive severity and response rate and narrower confidence intervals.

Figure 15. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, MDD/≤ 20 percent bipolar disorder



Meta-Analytic Synthesis of MDD and MDD/Bipolar mix Outcomes (Tiers 1, 2, and 3 Combined)

Meta-analyses combining studies from all tiers involved and including both MDD and MDD/bipolar mix populations continued to support the benefit of rTMS over sham control and were consistent with Tier 1 combined analyses. Most studies showed a significantly greater decrease in depressive severity in the rTMS group. The weighted mean difference in HAM-D depressive severity was -5.92 (95% CI, -8.15 to -3.70). Because sample sizes of individual studies were small and responses to placebo varied in the small control groups, the heterogeneity was high (I^2 = 80%) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

The pooled relative risk indicated that patients receiving rTMS were more than twice as likely to respond as those receiving placebo (pooled relative risk 2.68, 95% CI, 1.52-4.70) (Figure 16), which translates into a NNT of 5 (95% CI, 4-9). Remission rates also favored rTMS. The pooled relative risk for remission was 3.73 (95% CI, 1.23-11.30), which translates to an NNT of 6 (95% CI, 3-50) (Figure 17).

Compared to Tier 1 syntheses of MDD and MDD/bipolar populations combined, consideration of all three tiers provided more conservative point estimates and narrower confidence intervals for each outcome. Indeed, the meta-analytic results for MDD and MDD/bipolar mix for all tiers combined were most nearly identical to results for the Tier 1 MDD-only group, our main population of interest.

Figure 16. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, all populations

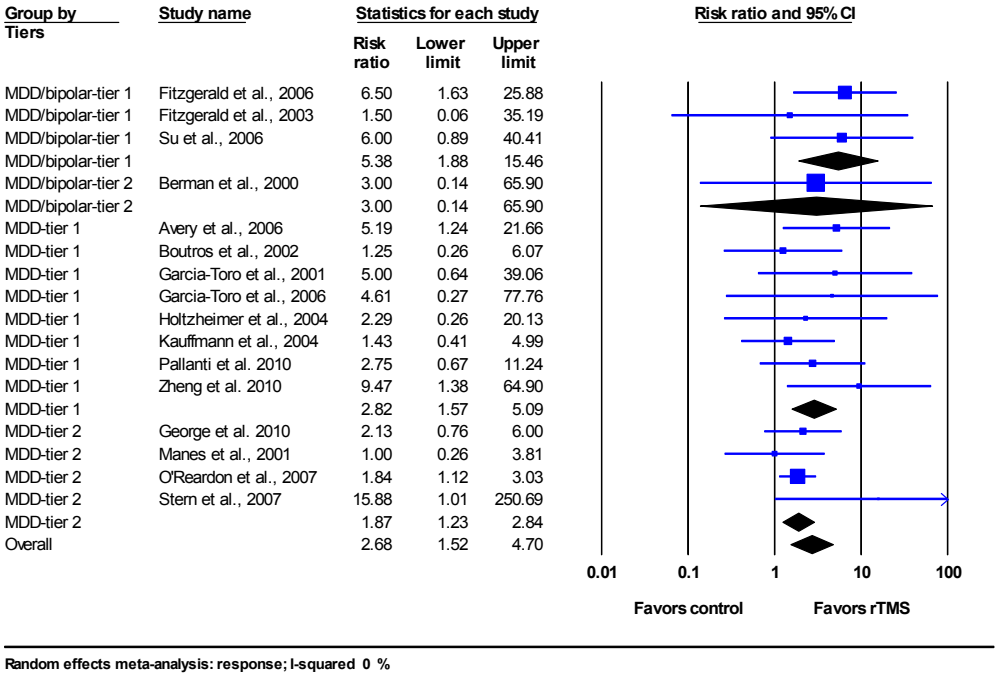
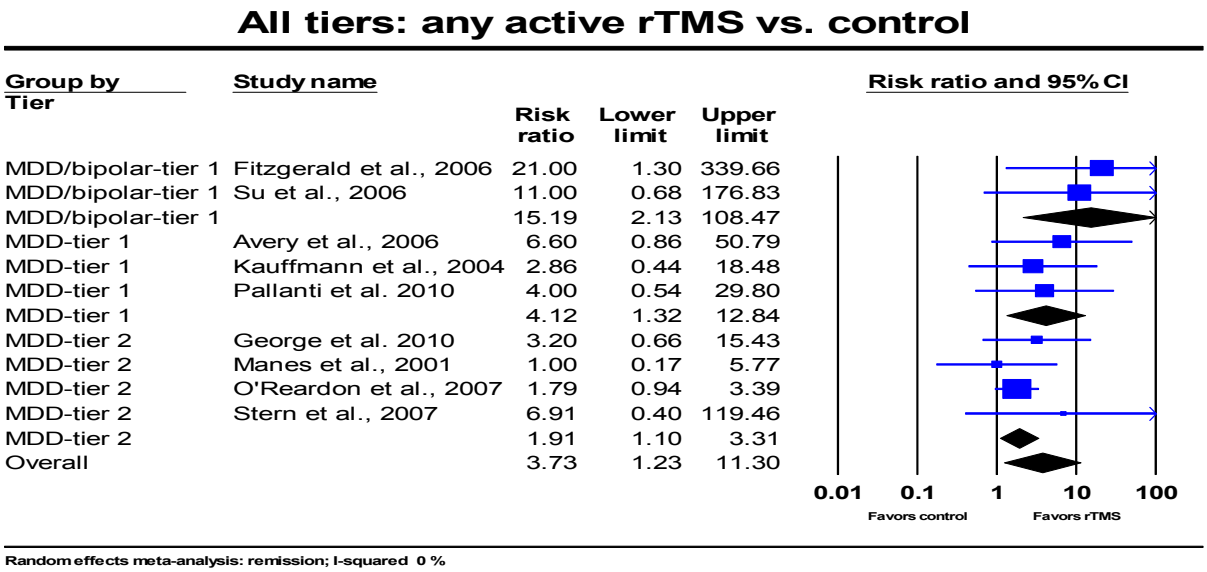


Figure 17. Relative risk meta-analysis of remission rates comparing rTMS with sham: Tiers 1 & 2, all populations



Summary of key Variables

Consideration of all tiers together for the combined MDD and MDD/bipolar mix populations provided results consistent with those from Tier 1 alone but with more conservative point estimates and narrower confidence intervals, suggesting that results from analyses of studies from all tiers reflect what can be expected in TRD (Tier 1) populations. This finding of all tier evidence reflecting what was found with Tier 1 alone held whether the population included was MDD-only or MDD/bipolar mix.

Results from Tiers 1–3 for MDD-only were in the same direction as and of similar magnitude to those for Tier 1–3 MDD/bipolar mix populations. For each outcome, point estimates for the MDD/bipolar mix group were higher with wider confidence intervals, but they were not significantly different from the MDD-only group. When these results were combined, confidence intervals were either equivalent or narrower than when the diagnostic samples were split, suggesting that combining MDD and MDD/bipolar presentations was reasonable.

Only three studies required an antidepressant failure in the current episode;[73,79,86] there was no clear variation in treatment efficacy between these studies and those not requiring a current episode failure.

At baseline almost all study populations had severe depression,[18,69-71,74-77,79-81,83,86-88,91] a few had moderate-to-severe depression,[72,73,84,85,90,92] and in one study population, severity was not reported.[78] With little variation in depression severity, we were unable to detect any differences by this variable.

In this comparison, 11 studies used an augmentation strategy,[18,69-75,79-81,90,92] 5 used a switch strategy,[76,84-88] 3 used a mixed strategy with within-group differences,[77,78,91] and 1 used a combination strategy with all patients starting a new antidepressant at study entry.[83] We were unable to detect clear differences by treatment characteristics (i.e., pharmacotherapy strategy, rTMS frequency, or treatment duration) through qualitative analysis due to other potentially confounding variables resulting from study design or participant characteristics.

Vagus Nerve Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

One trial comparing VNS plus treatment as usual with treatment as usual was identified in Tier 1 (Table 23).[98]

Table 23. Efficacy of VNS versus sham: Tiers 1-3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Rush et al., 2005[98] 10 weeks, m-ITT/per medication protocol Required failure in the current episode Good	**VNS (n = 119)** 10 weeks of VNS therapy with continued medications. **Sham (n = 116)** **Treatment strategy** Augmentation	**Diagnosis** Bipolar (%) VNS: 11.7 Sham: 9.1 **Number of failed antidepressant trials (% ≥ 4):** ECT: 46.5% rTMS: 40.0% **Baseline Depression** HAM-D_{24}, mean (SD) VNS: 28.8 (5.3) Sham: 29.7 (5.2)	**HAM-D_{24}*** % Change, mean (SD) VNS: -16.3 (28.1) Sham: -15.3 (25.5) *P* = 0.639 *based on VNS n = 112, sham n = 110	**HAM-D_{24}*** Response, n (%) VNS: 17 (15.2) Sham: 11 (10.0) *P* = 0.25

HAM-D_{24} = 24-item Hamilton Depression Scale; mITT = modified intention to treat; *P* = p-value; SD = standard deviation; VNS = vagus nerve stimulation

MDD-Only

There were no eligible studies.

MDD/Bipolar

One good 10-week study compared VNS (n = 119 patients) to a control group (n = 116 patients).[98] This study is summarized in Table 23 with a detailed description provided in the evidence tables (Appendix E). The control group had the surgical procedure to implant the VNS device, but they did not have the device turned on for the sessions. Patients were required to have had an unsatisfactory response to at least two adequate trials of antidepressant medication, but not more than six failures, for the current episode. More than 40 percent of the sample had four or more prior antidepressant treatment failures, indicating a high degree of treatment resistance. The two groups entering into this study were severely depressed, with a mean HAM-D_{24} score of 28.8 in the VNS group and 29.7 in the control. In a modified ITT analysis that excluded those noncompliant with the medication protocol, the results did not demonstrate a statistically significant difference between the two groups for the primary outcome (HAM-D_{24}). No differences were found in the percentage change in depressive severity (-16.3% for VNS vs. -15.3% for control, $P = 0.639$) or the response rates (15.2% vs. 10.0%, $P = 0.25$). Of note, response rates for a secondary outcome, the 30-item Inventory for Depressive Symptomatology-self report, favored VNS (17.0% vs. 7.3%, $P = 0.032$).

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined Results

Only one study comparing VNS to sham stimulation was identified.[98] This study is described in the section above.

Psychotherapy Versus Control

Tier 1: Patients With two or More Treatment Failures

There were no eligible studies.

Tier 2: Patients With one or More Failures

MDD-Only

Four Tier 2 studies[93-97] comparing psychotherapy to a control group were identified (Table 24). All indicated improvement with CBT. Only one of these studies received a good-quality rating.[95,96] Two studies used an augmentation strategy,[93,95,96] one used an unlimited strategy (patients in both groups may or may not start a new medication),[97] and the fourth study used a combination strategy with patients in all groups starting a new medication;[94]the type of treatment strategy produced no clear variation in outcome. The presence of treatment failure in the current episode did not clearly influence outcome. The duration of the trials (all 16–20 weeks) did not vary. Groups in all studies were moderately depressed.

One good 20-week RCT (described in 2 articles) compared 16 sessions of cognitive therapy and clinical management (CM) (n = 80 patients) to CM alone (n = 78 patients).[95,96] In each case, CM consisted of a visit with a psychiatrist every 4 weeks with minor medication adjustments to

an antidepressant medication regimen allowed. Patients entered the study having residual depressive symptoms (HAM-$D_{17} \geq 8$) despite having received greater than 4 weeks of adequate antidepressant treatment. Depression in both groups was mild (mean HAM-D_{17} for the two groups was 12.1-12.2). In an ITT analysis, there was no difference in the mean decrease in depressive severity (CBT plus CM -3.4 vs. CM alone -2.8, *P* = NS). Remission was defined more stringently as a HAM-D_{17} score ≤ 7 at two consecutive visits 4 weeks apart; using this definition, remission rates were greater for CBT plus CM when compared with CM alone (24% vs. 13%, $P < 0.05$).

One trial compared a 4-month treatment of CBT plus CM (n = 14 patients) to CM alone (n = 11 patients).[97] Mean depressive severity at baseline as measured by the BDI was 31.1 for CBT plus CM versus 26.8 for CM, consistent with depression that was moderate to severe. Usual care (UC) in each group resulted in unlimited medication strategy. In an ITT analysis, the CBT plus UC group reduced depressive severity as measured by the BDI by an average of 11.2 points more than the UC group (95% CI, -19.3 to -3.1). Also, the CBT plus UC group had eight patients meeting response criterion, compared to none in the UC group.

Table 24. Efficacy of psychotherapy versus control: Tiers 1-3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Harley, 2008[93] 16 weeks, completers analysis Tier 2: Failure not required in current episode Fair	**CBT [DBT] (n = 13)** 16 sessions of dialectical behavior therapy skill training **Control (n = 11)** Waitlist **Treatment strategy** Augmentation **Definitions** Remission definition: HAM-D_{17} score ≤ 7	**Mean number of failed antidepressant trials:** CBT: NR Control: NR **Baseline Depression** HAM-D_{17}, mean (SD) CBT: 16.15 (4.47) Control: 18.64 (4.72)	**HAM-D_{17}*** Change, mean (SD) CBT: -5.6 Control: -1.78 *P < 0.05* * results based on completers (CBT: n = 10, Control: n = 9)	**HAM-D_{17}** Remission (%) CBT: 3 (23.1) Control: 0 (0) *P* = NR
Kocsis et al., 2010[94] 12 weeks, completers analysis Tier 2: Required failure in the current episode Fair	**CBASP (n=200)** 16 to 20 sessions of cognitive behavioral analysis system of psychotherapy **BSP (n=195)** 16 to 20 sessions of brief supportive psychotherapy **No Psychotherapy (n=96)** **Treatment strategy** Combination (all patients received next option on pharamcotherapy algorithm including sertraline, escitalopram, buproprion, venlafaxine, mirtazapine, and lithium) **Definitions** Remission HAM-D_{24} < 8 AND 50% decrease from baseline	**Number of failed antidepressant trials:** Mean (SD) CBASP: NR BSP: NR No therapy: NR **Baseline Depression:** HAM-D_{24}, mean (SD) CBASP: 19.52 (8.56) BSP: 19.44 (8.31) No therapy: 18.37 (8.00)	**HAM-D_{24}** Change*, mean (SD) CBASP: -8.23 BSP: -6.67 No therapy: -6.09 *P* = NS *based on completers CBASP n= 174 BSP n = 168 No therapy n = 76	**HAM-D_{24}** Remission, n (%)* CBASP: 67 (33.5) BSP: 52 (26.7) No therapy: 30 (31.3) *P* = NS

Table 24. Efficacy of psychotherapy versus control: Tiers 1-3 (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Paykel, 1999[95] and Scott, 2000[96] 20 weeks Tier 2: Required failure in the current episode Good	**CBT (n = 80)** 16 sessions of cognitive therapy plus clinical management **CM (n = 78)** Clinical management alone **Treatment strategy** Primarily augmentation with minor medication dose adjustments allowed. **Definitions** Remission definition: HAM-D_{17} score ≤ 7 at 2 consectutive ratings 4 weeks apart	**Mean number of failed antidepressant trials:** CBT: NR CM: NR **Baseline Depression** HAM-D_{17}, mean (SD) CBT: 12.2 (2.9) CM: 12.1 (2.7)	**HAM-D_{17}** Change, mean (SD) CBT: -3.4 CM: -2.8 *P* = NS	**HAM-D_{17}** Remission, n (%) CBT: 19 (24) CM: 10 (13) Hazard Ratio for remission 2.42 (95% CI: 1.08 to 5.45), *P* = 0.03
Wiles et al., 2008[97] 4 months Tier 2: Required failure in the current episode Fair	**CBT plus CM (n = 14)** 12-20 sessions of cognitive behavioral therapy and clinical management **CM (n = 11)** Clinical management, no restrictions **Treatment Strategy** Unlimited	**Mean number of failed antidepressant trials:** CBT: NR CM: NR **Baseline Depression** BDI, mean (SD) CBT: 31.1 (8.5) CM: 26.8 (6.8)	**BDI** CBT scores decreased by an average of 11.2 points more than CM (95% CI, -19.3 to -3.1)	**BDI** Response, n (%) CBT: 8 (57.1) CM: 0 (0.0) *P* = NR

BDI = Beck Depression Inventory; BSP = Brief Supportive Therapy; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; CBT = cognitive behavioral therapy; CI = confidence interval; CM = clinical management; DBT = Dialectical Behavioral Therapy; HAM-D_{17} = 17-item Hamilton Depression Scale; n = number; NR = not reported; NS = not significant; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

One 12-week RCT compared 12 weeks of CBT plus pharmacotherapy (n = 200) with participants receiving pharmacotherapy alone (n = 96).[94] A third arm assessing Brief Supportive Therapy was included in the study but is not an intervention of interest for this report and is therefore not included in this description. Enrolled patients were required to have an inadequate response (i.e., HAM-$D_{24} \geq 8$) to their medication at baseline. At baseline patients had mild to moderate depression (HAM-D_{24}, mean [SD]: CBT 19.5 [8.6], no CBT (medication only): 18.37 [8.0]). The trial used a combination treatment strategy, starting patients in all groups on a new medication. In a completers analysis, no significant differences were found between groups for decrease in depressive severity or rates of remission.

One 4-month trial compared a distinct form of CBT that involves both group and individual treatments called Dialectical Behavioral Therapy (DBT) (n = 13 patients) to a wait list control (n = 11).[93] The two participating groups had moderate depressive severity at study enrollment (HAM-D_{17} scores averaged 16.15 for DBT group and 18.64 for waitlist control). In a treatment completer analysis at 4 months, the DBT group (n = 10) had a greater decrease in depressive severity than the waitlist group (n = 9) (-5.6 vs. -1.78, $P < 0.05$) and were more likely to achieve remission (23.1% vs. 0%).

We did not quantitatively synthesize these results.

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined Results

Four Tier 2 studies comparing psychotherapy to a control group were identified. One good study reported in two articles[95,96] and two fair studies[93,97] supported greater outcomes for patients in psychotherapy compared to a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.[94] Unlike the first three studies,[93,95-97] the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning.[94] Two of the studies used augmentation strategies[93,95,96] and another did not limit the pharmacotherapy strategies of participants.[97] With only four studies identified for this comparison, it is difficult to determine how study design, participant, or treatment characteristics may have affected treatment efficacy. All four studies fell into Tier 2 and three of the trials[94-97] required a failure in the current episode. All patients had MDD. Duration and method of psychotherapeutic interventions were similar across studies.

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Comparisons

In this section, we assess how nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms in patients with TRD; these comparisons can help place nonpharmacologic treatments for TRD within the context of pharmacologic ones. First, we review the literature that directly compares nonpharmacologic and pharmacologic interventions for TRD, using the same approach we did in KQ 1a: categorizing first by intervention comparison, next by tier, and then by MDD versus the MDD/bipolar mix, while considering the role of the same key elements on treatment outcome.

For nonpharmacologic versus pharmacologic comparisons, we identified three studies. One study compared ECT versus pharmacotherapy, and two compared CBT with pharmacotherapy. Only one of these studies involved a TRD (Tier 1) population; enrolling an MDD/bipolar mix sample, it provided data showing that switching to ECT provided a greater decrease in depressive severity than switching to a new pharmacotherapy.[66]

Considering Tier 2 studies added two trials comparing CBT versus pharmacotherapy, both in MDD-only populations.[101,102] These two studies involved moderately depressed groups and provided data showing that CBT was no different than medication treatments for a variety of treatment strategies.[101,102] We could not make any conclusions about the impact of tier definition, diagnosis, depressive severity, treatment strategy, treatment characteristics, or treatment failure in the current episode.

For pharmacologic versus pharmacologic treatments, we identified nine trials that used a variety of pharmacologic treatment strategies to treat TRD including switching to a new antidepressant medication[103-108] and augmenting the current medication.[109-111] All involved patients who were severely depressed. Response rates for the pharmacologic options did not clearly differ from CBT, but two studies reporting CBT outcomes versus medications did appear to have poorer outcomes than ECT in one study. Finally, mean remission rates for pharmacologic options were similar to those reported in nonpharmacologic studies.

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Nonpharmacologic Versus Pharmacologic Treatments

Only three studies providing nonpharmacologic versus pharmacologic treatments were available (Table 25).[66,101,102] Having such a limited database prevented a consideration of the effect on outcome of which tier of evidence was used, whether the population was MDD-only versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, and whether the treatment failure was in the current episode.

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. We first will present the strength of evidence for Tier 1 studies alone, and then present strength of evidence for all three tiers considered together. When possible, within each comparison we report results by treatment strategy since this is a fundamental aspect of the antidepressant therapy.

Table 25. Number of good- and fair-quality studies by comparison, tier, and diagnostic mix for KQ 1b

Comparison	Tier	MDD-only	MDD and Bipolar Disorder
ECT versus pharmacotherapy	Tier 1 (≥ 2 treatment failures)	0	1
Psychotherapy vs. pharmacotherapy	Tier 2 (≥ 1 treatment failures)	2	0

ECT = electroconvulsive therapy

A single MDD/bipolar mix study[66] suggested better outcomes for ECT compared with pharmacologic treatment. Two studies found no difference between CBT and pharmacologic options.[101,102]

Strength of Evidence: Tier 1 (TRD)

Only one study providing nonpharmacologic versus pharmacologic treatments was available.[66] Having such limitations prevented consideration of the effect on outcome whether the population was MDD versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, and whether the treatment failure was in the current episode.

Data were available to allow strength of evidence assessments for two outcomes: change in depressive severity and response rates (Table 26). This single trial provided low strength of evidence that ECT produced better outcomes than medications in a Tier 1 MDD/bipolar mix population; the study did not address remission rates.[66]

Table 26. Strength of Evidence: ECT versus pharmacotherapy

Comparison	Number of Studies; Subjects	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 39	Medium/ High RCT 1 fair	Unknown	Direct	Imprecise	ECT > pharmacotherapy (paroxetine) Low
Response	1; 39	Medium/ High RCT 1 fair	Unknown	Direct	Imprecise	ECT > pharmacotherapy (paroxetine). Low
Remission	0; 0	—	—	—	—	—

ECT = electroconvulsive therapy; RCT = randomized controlled trial

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Key Points of Nonpharmacologic Versus Pharmacologic Treatments

Only four trials provided a direct comparison of nonpharmacologic and pharmacologic treatment for TRD. The limited number of comparisons prevented any firm conclusions regarding the effect on outcome of the tier level of evidence used, whether the population was MDD-only versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, or whether the treatment failure was in the current episode.

Electroconvulsive Therapy Versus Pharmacotherapy

One Tier 1 study comparing ECT with pharmacotherapy found a greater change in depressive severity and a higher rate of response for participants in the ECT group.[66]

Cognitive Behavioral Therapy Versus Pharmacotherapy

One Tier 2 study comparing CBT with pharmacotherapy found no differences in change in depressive severity, rate of response, or rate of remission between groups.[101] A second study, with a small sample (N = 13), showed a difference in change in depressive severity but did not report the test of statistical significance.[102]

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Nonpharmacologic Versus Pharmacologic Treatments

Electroconvulsive Therapy Versus Pharmacotherapy

Tier 1: Patients With two or More Treatment Failures

One study comparing ECT to pharmacotherapy in an MDD/bipolar mix population was identified for Tier 1 (Table 27), finding greater improvement in severity and response for patients receiving ECT versus paroxetine.

MDD-Only

There were no eligible studies.

MDD/Bipolar

One 4-week trial compared outcomes for right-sided unilateral ECT (n = 21 patients) with paroxetine (n = 18 patients, 22 randomized).[66] All patients discontinued current antidepressant therapy, and patients in the paroxetine group initiated pharmacotherapy. In the ECT group, 9.5 percent of patients (n = 2) had bipolar illness; 16.7 percent (n = 3) had bipolar illness in the medication group. Patients were severely depressed (mean HAM-D_{21} scores were 31.1 in the ECT group (SD 4.9) and 32.8 (SD 5.4) in the pharmacotherapy group). The ECT group experienced a greater decrease in depressive severity (-18.6 vs. -9.6, *P* = 0.001) and a greater response rate (71.4% vs. 27.8%, *P* = 0.006) than the paroxetine group.

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined

Only one study comparing ECT to pharmacotherapy was identified;[66] this study is described in the section above.

Table 27. Efficacy of ECT versus pharmacotherapy: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Folkerts et al., 1997[66] End of study phase (2-4 weeks), per protocol analysis Tier 1: Did not require failure in the current episode Fair	**ECT (n = 21*)** Right unilateral, mean txts = 7.2 sessions (2-3 weeks) **Pharmacotherapy (n = 18*)** Paroxetine 40 mg (max 50 mg/d, mean 44 mg/day) *per protocol **Treatment Strategy** Switch	**Diagnosis** Bipolar (%) ECT: 9.5 Pharm: 16.7 **Mean number of failed antidepressant trials:** ECT: 4.9 Pharm: 4.3 **Baseline Depression** HAM-D_{21}, mean (SD) ECT: 31.1 (4.9) Pharm: 32.6 (5.4)	**HAM-D_{21}** Change, mean (SD) ECT: -18.6 Pharm: -9.6 *P* = 0.001	**HAM-D_{21}** Response, n (%) ECT: 15 (71.4) Pharm: 5 (27.8) *P* = 0.006

ECT = electroconvulsive therapy; ; HAM-D_{21} = 21-item Hamilton Depression Scale; max = maximum, mg = milligram; mg/d = milligram per day; n = number; *P* = p-value; pharm = pharmacotherapy; SD = standard deviation; txt(s) = treatment(s)

Cognitive Behavioral Therapy Versus Pharmacotherapy

Two Tier 2 studies, both MDD-only, compared psychotherapy versus pharmacotherapy and are described in Table 28. Both studies required an antidepressant failure in the current episode

and used mixed strategies with between-group differences. One study compared augmenting to switching; the second study required that patients randomized to psychotherapy discontinue medications and compared this group to those who continued their antidepressant medications. Studies were similar in duration so no comparison by study duration was made.

Tier 1: Patients With two or More Treatment Failures

There were no eligible studies.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

One study used a randomization strategy that considered patient choice. Sixteen sessions of cognitive therapy were compared to medication treatment as either an augmentation strategy (each was added to citalopram treatment, respectively) or a switch strategy (changed to CT or a different medication treatment).[101] Patients entering all arms were of moderate severity (QIDS-SR mean 11 to 12). Using an ITT analysis, no differences in percentage change in depressive symptomatology were found when comparing CT to medication in either the augmentation (-29.5% vs. -28.3%, $P = 0.8302$) or switch (-15.6% vs. -17.2%, $P = 0.9040$) strategy comparisons. For patients who received augmentation to their citalopram, the response rate did not differ for those to whom CT was added (n = 65 patients) versus those to whom medication was added (n = 117 patients) (35.4% vs. 28.2%, $P = 0.2493$). Similarly, the response rate did not differ between those who switched to CT (n = 36 patients) compared to those who switched to a different medication (n = 86 patients) (22.2% vs. 26.7%, $P = 0.8390$). As with change in severity and response, no differences between cognitive therapy and pharmacotherapy were found in remission between groups in the augmentation ($P = 0.7803$) or switch group comparisons ($P = 0.9032$).

One small study[102] randomized patients to either switch to 4 months of CBT (n = 7) or continue their current medication management (n = 6). Enrolled patients had moderate depressive severity (mean HAM-D score at baseline 18.6 for CBT [SD 3.3] and 18.3 [SD 3.9] for medication). A limited treatment completer's analysis of acute phase outcomes at 4 months suggested a greater decrease in severity for the CBT group (-7.6 points [n = 5 patients] vs. +1.5 points [n = 4 patients], statistical analysis not reported).

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1–3: Combined Results

Only two studies were identified for this comparison.[101,102] Although one study did not find differences between groups in treatment efficacy (i.e., change in severity, response, and remission),[101] the second study showed a difference in change in depressive severity but did not report the results of a test of statistical significance.[102] Both studies were identified in Tier 2, required a failure in the current episode, included only patients with MDD, included samples with moderate depressive severity, and used similar treatment characteristics (i.e., both used

cognitive behavioral therapy and were approximately 4 months in duration). The first study compared treatment arms that augmented with either psychotherapy or a new antidepressant medication and arms that switched to psychotherapy or a new antidepressant.[101] The second study compared switching to psychotherapy to continued medication management.[102]

Table 28. Efficacy of psychotherapy versus pharmacotherapy: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Thase et al., 2007[101] 12-14 weeks Required failure in the current episode Fair	**Augmentation - Cognitive Therapy (n = 65)** Continued citalopram and added CT (16 sessions in 12 weeks) **Augmentation - Medication (n = 117)** Citalopram plus buproprion SR or buspirone **Switch - Cognitive Therapy (n = 36)** Switch from citalopram to CT 16 sessions in 12 weeks **Switch - Medication (n = 86)** Switch from citalopram to sertraline, bupropion SR, or extended-release-XR **Treatment strategy** Mixed-between group differences **Definitions** Remission defined as QIDS-SR ≤ 5	**Mean number of failed antidepressant trials:** Aug CT: NR Aug Med: NR Switch CT: NR Switch Med: NR **Baseline Depression** QIDS-SR, mean (SD) Aug CT: 11.9 (4.3) Aug Med: 12.0 (4.6) Switch CT: 11.2 (4.3) Switch Med: 12.1 (4.6)	**QIDS-SR** % Change, mean (SD) Aug CT: -29.8 (40.5) Aug Med: -28.3 (39.6) *P* = 0.8302 Switch CT: -15.6 (40.7) Switch Med: -17.2 (46.2) *P* = 0.9040	**QIDS-SR** Response, n (%) Aug CT: 23 (35.4) Aug Med: 33 (28.2) *P* = 0.2493 Switch CT: 8 (22.2) Switch Med: 23 (26.7) *P* = 0.8390 Remission, n (%) Aug CT: 20 (30.8) Aug Med: 39 (33.3) *P* = 0.7803 Switch CT: 11 (30.6) Switch Med: 23 (26.7) *P* = 0.9032
Moore et al., 1997[102] 4 months is closest to end of treatment, completers analysis Required failure in the current episode Fair	**Cognitive Behavioral Therapy (n = 7)** minimum of 4 txts 1st month, 2 txts 2nd month and 1 per month following **Continued medication management (n = 6)** Continued medication dose within recognized therapeutic theshold **Treatment Strategy** Mixed- between group differences	**Mean number of failed antidepressant trials:** CBT: NR Meds: NR **Baseline Depression** HAM-D_{17}*, mean (SD) CBT: 18.6 (3.3) Meds: 18.3 (3.9) *Completers only (CBT n = 5, Meds n = 4)	**HAM-D_{17}** Change*, mean (SD) CBT: -7.6 Meds: +1.5 *Completers only *P* = NR	**HAM-D_{17}** Response: NR at end of txt Remission: NR at end of txt

CT = cognitive therapy; CBT = cognitive behavioral therapy; ; HAM-D_{17} = 17-item Hamilton Depression Scale; Meds = continued medication management; n = number; NR = not reported; *P* = p-value; QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report; SD = standard deviation; SR = sustained release; txt = treatment; XR = extended release

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Overview of Pharmacologic Versus Pharmacologic Treatments

All studies reviewed in this section are RCTs that involve Tier 1 TRD (≥ 2 failures of adequate antidepressant trials) and MDD-only patients. This synthesis allows a crude comparison between what one might expect as a "next-step" pharmacologic intervention relative to a next-step nonpharmacologic intervention. Consequently, these studies may provide a reference for the degree of response (or remission) that one could expect from a next-step pharmacologic treatment (relative to a next-step nonpharmacologic treatment).

Some of these studies include a group that did not receive an active primary antidepressant treatment (e.g., olanzapine, which by itself is not used as an antidepressant); these arms will not be considered in the subsequent analyses. We focus instead on the same three outcomes addressed in previous sections—change in depressive severity, response rate, and remission rate. However, we will not formally assess strength of evidence as we did in the prior sections. Rather, we will present the available clinical response data that illustrate what is expected following an active antidepressant treatment. We will consider both responses seen after a change in pharmacologic treatment (either a switch or augmentation) and responses seen after maintenance on the same pharmacologic management without a change in treatment. Finally, also in contrast to our prior sections, we will not consider the role of MDD/bipolar mix or tier definition, as these variables are by definition fixed in this section, but we will attempt to consider the other key elements.

We identified 12 Tier 1 MDD-only studies involving moderately to severely depressed groups that compared pharmacologic treatment as a next treatment step (Table 29).[103-114] We attempted to determine mean effect sizes, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, there were no comparable, common control groups not receiving a mood-related medication to allow such comparisons. Instead, we determined mean average outcomes for pharmacologic treatments. Although we were unable to statistically compare these outcomes, there was broad overlap in their decreases in depressive severity, relative risks of response, and relative risks of remission.

Table 29. Number of good- and fair-quality studies by comparison and definition of treatment resistance (tier) for MDD-only for KQ 1b

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
Pharmacotherapy versus Pharmacotherapy	Tier 1 (≥ 2 treatment failures)	12	NA
Pharmacotherapy versus Pharmacotherapy	Tier 2 (≥ 1 treatment failures)	NA	NA
Pharmacotherapy versus Pharmacotherapy	Tier 3 (probable treatment failure)	NA	NA

MDD = major depressive disorder; NA = not applicable

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Key Points of Direct Comparisons

All studies included in the pharmacologic intervention versus pharmacologic intervention were conducted in patients with MDD-only TRD. We identified 12 studies: 7 studies primarily tested switch strategies[103-108,112] and 5 assessed augmentation.[109-111,113,114] Seven of the 12 studies

also included a maintenance arm, allowing further analysis of this strategy as well. To allow comparison to the nonpharmacological interventions, weighted means were calculated for each strategy for the three outcomes of interest.

Regarding changes in depressive severity, mean changes in MADRS scores were similar across the three strategies (switch -11.2 [95% CI, -14.7 to -7.8], augmentation -11.2 [95% CI, -13.7 to -8.8], and maintenance -7.6 [95% CI, -9.2 to -5.2]). Consistent results were seen for response and remission rates (switch 39.8% [95% CI, 30.7-48.9] and 22.3% [95% CI, 16.2-28.4], augmentation 38.1% [95% CI, 31.0-45.3] and 27.2% [95% CI, 20.4-34.0], maintenance 27.3% [95% CI, 19.8-34.8] and 16.8% [95% CI, 13.5-20.2], respectively). These data are limited by the combination of different types of antidepressants and augmenting options included in this analysis.

Only one study did not require a failure in the current episode[110] limiting further analysis by this variable. Though some variability in the depressive severity of populations was present, differences by severity were not apparent.

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Direct Comparisons

Tier 1: Patients With two or More Treatment Failures

Twelve studies were identified for this population. Seven of the studies used switch strategies[103-108,112] and five tested an augmentation strategy.[109-111,113,114]

Switching Strategies

Seven studies testing a switch strategy were identified and are described in Table 30.[103-108,112] One study compared the 12-week outcomes for patients who failed venlafaxine treatment and were randomized to one of five groups: a combination of olanzapine (either 6 or 12 mg/day)/fluoxetine (either 25 or 50 mg/day) (n = 243 patients, pooled from 4 groups), olanzapine alone (either 6 or 12 mg/day) (n = 62 patients), fluoxetine alone (either 25 or 50 mg/day) (n = 60 patients), a "pseudo placebo" low-dose combination of olanzapine (1mg/day) and fluoxetine (5 mg/day) (n = 59 patients), or continuing with venlafaxine alone (75-375 mg/day) (n = 59 patients).[103] Only one treatment failure was required in the current episode (failure to respond to venlafaxine). Baseline depressive severity for the overall sample was in the moderate-to-severe range (MADRS 30.0). An ITT analysis favored the olanzapine/fluoxetine combination versus fluoxetine alone in all depression outcome comparisons, but showed no difference between any of the other groups. The combination was better than fluoxetine alone for greater change in depressive severity (-14.06 vs. -7.71, $P < 0.001$; other severity changes ranged from -11.7 to -13.73), greater response rate (43.3% vs. 25.4%, $P = 0.017$; other response rates ranged from 33.9% to 50.0%) and greater remission rate (29.9% vs. 13.8%, $P = 0.013$; other remission rates ranged from 17.9% to 22.4%).

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Corya et al., 2006[103] 12 weeks Required failure in the current episode Fair	**OLA-FLU (n = 243)** Combined 4 groups **OLA (n = 62)** 6 or 12mg/d **FLU (n = 60)** 25 or 50 mg/d **VEN (n = 59)** 75-375mg/d **LD OLA plus FLU (n = 59)** 1mg/d OLA, 5mg FLU **Treatment strategy** OLA-FLU: Switch OLA: Not of interest FLU: Switch VEN: Maintenance LD OLA-FLU: Switch **Definitions** Remission defined as MADRS ≤ 8 at two consecutive visits	**Baseline Depression** MADRS, mean (SD) Overall: 30.0 (6.8)	**MADRS** Change, mean (SD) OLA-FLU: -14.06 (0.59) OLA: -7.71 (1.17) FLU: -11.70 (1.14) VEN: -13.73 (1.16) LD OLA-FLU: -11.97 (1.13) OLA-FLU versusOLA *P* < 0.001 all others NS	**MADRS** Response, n (%) OLA-FLU: 100 (43.3) OLA: 15 (25.4) FLU: 19 (33.9) VEN: 29 (50.0) LD OLA-FLU: 20 (36.4) OLA-FLU versus OLA, *P* = 0.017 All others NS Remission, n (%) OLA-FLU: 69 (29.9) OLA: 8 (13.8) FLU: 10 (17.9) VEN: 13 (22.4) LD OLA-FLU: 11 (20.0) OLA-FLU versus OLA, *P* = 0.013. All others NS
Fang et al., 2010[112] 8 weeks, ITT Required failure in the current episode Fair	**MIR (n = 55)** 45mg/day **PAR (n = 45)** 20 mg/day **VEN (n = 50)** 225mg/day **Treatment strategy** MIR: Switch PAR: Switch VEN: Switch **Definitions** Remission: HAM-D_{17} ≤ 7	**Baseline Depression** HAM-D_{17}, mean (SD) Overall: 24.6 (5.8)	**HAM-D_{17}** Change, mean (SD) NR	**HAM-D_{17}** Response, n (%) MIR: 32 (58.2) PAR: 30 (66.7) VEN: 32 (64.0) *P* = 0.664 Remission, n (%) MIR: 20 (36.4) PAR: 21 (46.7) VEN: 21 (42.0) *P* = 0.578
Fava et al., 2006[104] 14 weeks Required failure in the current episode Good	**MIR (n = 114)** Up to 60 mg/d **NOR, (n = 121)** Up to 200 mg/d **Treatment strategy** MIR: Switch NOR: Switch **Definitions** Remission defined as HAM-D_{17} ≤ 7	**Baseline Depression** HAM-D_{17}, mean (SD) MIR: 19.8 (7.0) NOR: 18.6 (5.9)	**HAM-D_{17}** Change: NR	**HAM-D_{17}** Remission, n MIR:14 (12.3) NOR: 24 (19.8) *P* = 0.27
Mazeh et al., 2007[105] 6 weeks* only in the elderly Required failure in the current episode Fair	**PAR (n = 15)** 10-60 mg/d, mean = 26mg/d **VEN (n = 15)** 75-300 mg/d, mean = 165mg/d **Treatment strategy** PAR: Switch VEN: Switch **Definitions** Remission defined as HAM-D_{21} ≤ 7	**Baseline Depression** HAM-D_{21}, mean (SD) PAR: 30.1 (7.9) VEN: 26.3 (5.9)	**HAM-D_{21}** Change, mean (SD) PAR: -12.5 VEN: -19.1 *P* < 0.0003	**HAM-D_{21}** Response, n (%) PAR: 8 (53) VEN: 12 (80) *P* = NR Remission, n (%) PAR: 5 (33) VEN: 9 (60) *P* = NR

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1 (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
McGrath et al., 2006[106] 12 weeks Required failure in the current episode Good	**TRAN (n = 58)** 10 mg/d for 2wk, weekly increases of 10 mg/d until intolerance or 60 mg/dmaximum **VEN ER plus MIR (n = 51)** VEN - 37.5mg/d week 1, 75mg/d week 2, 150 mg/day weeks 3-5, 225 mg/d weeks 6-8, 300 mg/dthereafter MIR—15mg/d weeks 1-2, 30 mg/d next 8 weeks, 45mg/d thereafter **Treatment strategy** TRAN: Switch VEN-MIR: Switch **Definitions** Remission defined as HAM-D_{21} ≤ 7	**Baseline Depression** HAM-D_{17}, mean (SD) TRAN: 19.6 (7.6) VEN-MIR: 19.7 (5.5)	**HAM-D_{17}** Change: NR	**HAM-D_{17}** Remission, n (%) TRAN: 4 (6.9) VEN-MIR: 7 (13.7) *P* = NS
Poirier and Boyer, 1999[107] 4 weeks Required failure in the current episode Fair	**VEN (n = 61)** 37.5mg/twice day, increased to 200 - 300 mg/d **PAR (n = 62)** initiated at 20 mg/day and increased to 30—40 mg/d **Treatment strategy** VEN: Switch PAR: Switch **Definitions** Remission defined as HAM-D_{17} < 10	**Baseline Depression** HAM-D_{17}, mean (SD) VEN: 24.6 (3.9) PAR: 24.5 (4.1)	**HAM-D_{17}** Change*, mean (SD) VEN: -11.1 (8.5) PAR: -10.2 (6.8) *P* = 0.55 ITT, *P* = 0.70 *N observed (VEN: 52, PAR: 55)	**HAM-D_{17}** Response, n VEN: 27 (44.3) PAR: 18 (29.0) ITT, *P* = 0.07 Remission, n VEN: 22 (36.1) PAR: 11 (17.7) ITT, *P* = 0.02

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1 (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Shelton et al., 2005[108] 8 weeks Did not require failure in the current episode Good	**OLA-FLU combination (n = 146)** 6 mg/d OLA plus 25mg/d FLU or 12mg/d OLA plus 50 mg/d FLU **OLA (n = 144)** 6-12mg/d **FLU (n = 142)** 25 to 50 mg/d **NOR, (n = 68)** Max dose 175mg/d **Treatment strategy** OLA+FLU: Switch OLA: Not of interest FLU: Switch NOR: Maintenance	**Baseline Depression** MADRS, mean (SD) OLA-FLU: 28.5 (7.5) OLA: 28.4 (7.3) FLU: 28.4 (7.3) NOR: 28.8 (6.5)	**MADRS** Change, mean (SE) OLA-FLU: -8.71 (0.70) OLA: -6.95 (0.71) FLU: -8.51 (0.70) NOR: -7.46 (0.98 FLU versus OLA-FLU, *P* = 0.841 OLA versus OLA-FLU, *P* = 0.77	**MADRS** Response, n (%) OLA-FLU: 40 (27.5) OLA: 27 (19.3) FLU: 41 (28.9) NOR: 20 (30.3) *P* = 0.18 Remission, n (%) OLA-FLU: 24 (16.9) OLA: 18 (12.9) FLU: 18 (13.3) NOR: 12 (18.2) *P* = 0.62

FLU = fluoxetine; HAM-D_{17} = 17-item Hamilton Depression Scale; HAM-D_{21} = 21-item Hamilton Depression Scale; ER = extended release; ITT = intention to treat; LD = low-dose; OLA = olanzapine; MADRS = Montgomery-Asberg Depression Rating Scale; mg/d = milligrams per day; MIR = mirzapine; n = number; NOR = nortiptyline; NR = not reported; NS = not significant; OLA-FLU = olanzapine/fluoxetine; PAR = paroxetine; SD = standard deviation; TRAN = tranylcypromine; VEN = venlafaxine; wk = week

A fair 8-week study compared switching to one of three antidepressants: mirtazapine (n = 55), paroxetine (n = 55), or venlafaxine (n = 50). Patients were required to have at least one treatment failure in the current episode and were severely depressed at baseline (mean HAM-D_{17} 24.6). In an ITT analysis, response and remission rates did not differ between groups.

A good-quality study lasting 12–14 weeks compared switching to mirtazapine (up to 60 mg/day; n = 114 patients) or nortriptyline (up to 200 mg/day; n = 121 patients) in a group of patients who had two adequate antidepressant treatment failures in the current episode.[104] Enrolled patients were severely depressed at baseline (mean HAM-D_{17} 18-20). Response rates as measured by the QIDS-SR did not differ significantly (13.4% for mirtazapine vs. 16.5% for nortriptyline). Similarly, remission rates did not differ significantly between the mirtazapine and nortriptyline groups (12.3% vs. 19.8%, *P* = 0.27).

A 6-week study compared outcomes for patients 65 years and older who were randomized to receive venlafaxine (75 mg to 300 mg/day, mean daily dose 165 mg/day; n = 15 patients) or paroxetine (10-60 mg/day, mean 26 mg/day; n = 15 patients).[105] Patients had two failures of adequate trials during the current episode and were severely depressed at study entry (mean HAM-D_{21} 26-30). In an ITT analysis, the decrease in depressive severity after 6 weeks was greater for venlafaxine than paroxetine (-19.1 vs. -12.5, *P* < 0.0003). Differences between response rates (80% vs. 53%, *P* = NR) and remission rates (60% vs. 33%) in this small sample was less clear.

One study compared 12-week outcomes for patients with treatment failure following three adequate antidepressant treatments in the current episode. Patients were randomized to

tranylcypromine (10 mg to 60 mg/day) (n = 58 patients) or a combination of venlafaxine ER (37.5 mg to 300 mg/day) plus mirtazapine (15 to 45 mg/day) (n = 51 patients).[106] Patients were severely depressed at study entry (mean HAM-D_{17} 19-20). Outcomes tended to favor the venlafaxine/mirtazapine combination, but not to a statistically significant degree. In an ITT analysis, response rates (as measured by the QIDS-SR) did not significantly differ (12.1% with tranylcypromine vs. 23.5% with venlafaxine plus mirtazapine), nor did the remission rates measured by HAM-D_{17} (6.9% vs. 13.7%).

Another venlafaine/paroxetine study compared 200–300 mg/day of venlafaxine (n = 61 patients) to 30–40 mg/day of paroxetine (n = 62 patients) for 4 weeks.[105] Patients had treatment failure following two adequate treatments other than venlafaxine or paroxetine in the current episode. Enrolled patients were severely depressed at study entry (mean HAM-$D_{24\text{-}25}$). The authors conducted an ITT analysis. The change in depressive severity did not differ between the two groups. However, the response rate tended to favor venlafaxine (44.3% vs. 29.0%, $p = 0.07$), and the remission rate supported venlafaxine over paroxetine (36.1% vs. 17.7%, $P = 0.02$).

Another olanzapine/fluoxetine switch study compared the 8-week outcomes for four groups following nortriptyline treatment failure: a combination of olanzapine (6 mg/day or 12 mg/day)/fluoxetine (25 mg/day or 50 mg/day) (n = 146 patients), olanzapine alone (6–12 mg/day) (n = 144 patients), fluoxetine alone (25–50 mg/day) (n = 142 patients), and continuing on nortriptyline alone (50–175 mg/day) (n = 68 patients).[108] Only one treatment failure was required to be in the current episode (failure to respond to nortriptyline). Baseline depressive severity for each group averaged between 28 and 29 on the MADRS, consistent with moderate-to-severe depressive severity. A mixed-effects model repeated-measures regression showed no differences between the four groups in decrease in depressive severity (-8.71, -6.95, -8.51, and -7.46, respectively, P = NS), response rates (27.5%, 19.3%, 28.9%, and 30.3%, respectively, $P = 0.18$), or remission rates (16.9%, 12.9%, 13.3%, 18.2%, respectively, $P = 0.62$).

Augmenting Strategies

Five studies tested augmenting strategies and are described in Table 31.[109-111,113,114] Two fair studies assessing the efficacy of augmenting with ariprprazole were identified.[113,114] Patients in both studies had a failed antidepressant trial in the current episode with 2 or more failures overall and were moderately depressed at baseline (mean MADRS [SD]: study 1[113]: ARI 26.0 [6.1] placebo 25.9 [6.5]; study 2[114] ARI 26.6 [5.8] placebo 27.1 [5.8]). In modified ITT analyses, both studies found significantly greater outcomes for ARI when compared with placebo across all three outcomes of interest.[113,114]

Table 31. Efficacy of pharmacotherapy versus control, augmenting strategies

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Berman et al., 2007[113] 6 weeks, mITT Required failure in the current episode Fair	**ARI (n = 184)** **Placebo (n = 178)** **Treatment strategy** ARI: Augmentation Placebo: Maintenance All patients receiving ESC, FLU, PAR, SER, VEN at maximum tolerated dose; ARI (2-20 mg/day) **Definitions** Remission defined as MADRS < 10 and ≥ 50% decrease in score	**Baseline Depression** MADRS, mean (SD) ARI: 26.0 (6.1) Placebo: 25.9 (6.5)	**MADRS** Change*, mean (SD) ARI: -8.8 Placebo: -5.8 *P* < 0.001 *mITT ARI N = 181 Placebo: 172	**MADRS** Response, n (%) ARI: 61 (33.2) Placebo: 41 (23.0) * *P* ≤ 0.05 Remission, n (%) ARI: 47 (25.5) Placebo: 27 (15.2) * *P* ≤ 0.01
Berman et al., 2009[114] 6 weeks, mITT Required failure in the current episode Fair	**ARI (n = 177)** **Placebo (n = 172)** Same antidepressant medications as above **Treatment strategy** ARI: Augmentation Placebo: Maintenance All patients receiving ESC, FLU, PAR, SER, VEN at maximum tolerated dose; ARI (2-20 mg/day) **Definitions** Remission defined as MADRS < 10 and ≥ 50% decrease in score	**Baseline Depression** MADRS, mean (SD) ARI: 26.6 (5.8) Placebo: 27.1 (5.8)	**MADRS** Change*, mean (SD) ARI: -10.1 Placebo: -6.4 *P* < 0.001 *mITT ARI: N = 174 Placebo: N = 169	**MADRS** Response, n (%) ARI: 81 (45.8) Placebo: 45 (26.2) * *P* ≤ 0.001 Remission, n ARI: 64 (36.2) Placebo: 32 (18.6) **P* ≤ 0.001
Nierenberg et al., 2003[109] 6 weeks Required failure in the current episode Fair	**LITH Augmentation (n = 18)** Dosing strategy NR **Placebo (n = 17)** All patients continued nortriptyline **Treatment strategy** LITH: Augmentation Placebo: Maintain	**Baseline Depression** HAM-D_{21}, mean (SD) LITH: 18.8 Placebo: 19.8	**HAM-D_{21}** Change, mean (SD) LITH: -2.9 Placebo: -3.6 *P* = NR	**HAM-D_{21}** Response, n (%) LITH: 2 (11.1) Placebo: 3 (17.6) *P* = NS
Shelton et al., 2001[110] 8 weeks Required failure in the current episode Fair	**OLA+ Placebo (n = 8)** 5-20 mg/d **FLU+ Placebo (n = 10)** 20-60 mg/d **OLA+FLU (n = 10)** same dose as above **Treatment strategy** OLA+PLA: Not of interest FLU+PLA: Maintain OLA: Augmentation	**Baseline Depression** MADRS: NR	**MADRS** Change, mean (SD) OLA+ Placebo: -2.8 FLU+ Placebo: -1.2 OLA+FLU:-13.6	**MADRS** Response, n (%) OLA+ Placebo: 0 (0) FLU+ Placebo: 1 (10) OLA+FLU: 6 (60) OLA-FLU versus OLA+ Placebo, *P* = 0.03 OLA+FLU versus FLU+ Placebo, *P* = 0.11

Table 31. Efficacy of pharmacotherapy versus control, augmenting strategies (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Thase et al., 2007[111] 8 weeks Required failure in the current episode Fair	**OLA+FLU (n = 200)** OLA 6, 12, or 18 mg/day plus 50 mg/day FLU **OLA (n = 206)** 6, 12, or 18 mg/day **FLU (n = 200)** 50 mg/day **Treatment strategy** OLA-FLU: Augmentation OLA: Not of interest (Switch) FLU: Maintain	**Baseline Depression** MADRS, mean (SD) OLA+FLU: 30.0 (6.7) OLA: 29.9 (6.4) FLU: 29.9 (6.7)	**MADRS** Change, mean (SD) OLA+FLU: -12.6 (10.3) OLA: -9.2 (9.7) FLU: -8.9 (9.0) OLA+FLU versus OLA, *P* < 0.001 OLA+FLU versus FLU, *P* < 0.001	**MADRS** Response, n (%) OLA+FLU: 80 (40.4) OLA: 60 (29.6) FLU: 51 (25.9) OLA+FLU versus FLU, *P* = 0.028 OLA+FLU versus FLU, *P* = 0.003 Remission, n (%) OLA+FLU: 54 (27.3) OLA: 34 (16.7) FLU: 29 (14.7) OLA+FLU versusFLU, *P* = 0.012 OLA-FLU versus FLU, *P* = 0.003

ARI = aripriprazole; ESC = escitalopram; FLU = fluoxetine; HAM-D_{21} = 21-item Hamilton Depression Scale; LITH = lithium, n = number; MADRS = Montgomery-Asberg Depression Rating Scale; mg/d = milligrams per day; mITT = modified intention to treat; NR = not reported; NS = not significant; OLA = olanzapine; OLA-FLU = olanzapine+fluoxetine; OLA+PLA = olanzapine plus placebo; PAR = paroxetine; SD = standard deviation; SER = sertraline; VEN = venlafaxine

Another study compared outcomes at 6 weeks for patients who had not responded to a 7-week nortriptyline trial and were assigned to augment nortriptyline with either lithium (dose not clarified; n = 18 patients) or placebo (n = 17 patients).[109] Prior to their nortriptyline trial, they had at least one but no more than five treatment failures following antidepressant medication treatment during the current episode. Patients were moderately depressed at study entry (mean HAM-$D_{17\text{-}18}$). In an ITT analysis, change in depressive severity did not differ between groups (-2.9 for lithium augmentation vs. -3.6 for placebo, $P = 0.72$). Similarly, response rates did not differ significantly for lithium augmentation versus placebo augmentation (11.1% vs. 17.6%, *P* = NS).

A third study compared outcomes at 8 weeks for patients who had two treatment failures to different classes of antidepressants and had an additional failed trial of fluoxetine in the current episode. These patients were assigned to either switch to olanzapine (5 to 20 mg/day; n = 8 patients), add olanzapine (5 to 20 mg/day) to fluoxetine (20 to 60 mg/day) (n = 10 patients) or continue with fluoxetine (50 mg/day) with placebo added (n = 10 patients).[110] Baseline mean depressive severity was not reported. The olanzapine/fluoxetine augmentation group had a greater decrease in HAM-D_{21} items severity than either the olanzapine switch group (-11.7 vs. -5.9, $P = 0.03$) or the fluoxetine continuation group (-11.7 vs. -3.8, $P = 0.07$). The olanzapine/fluoxetine augmentation group also had a greater response rate than the olanzapine switch group (60% vs. 0%, $P = 0.03$) and a trend towards greater response than the fluoxetine continuation group (60% vs. 10%, $P = 0.11$).

Lastly, a study that consisted of two parallel, concurrent trials compared the 8-week outcomes of an olanzapine/fluoxetine combination (6, 12, or 18 mg olanzapine plus 50 mg/day of fluoxetine; n = 200 patients), olanzapine (6, 12, or 18 mg/day; n = 199 patients), or fluoxetine

(50 mg/day; n = 206 patients).[111] The pooled analyses are reported here. Treatment failure was in the current episode. Patients entering the study were moderately to severely depressed (MADRS score of approximately 30). ITT analyses at study end favored the combination treatment relative to the other two groups in each instance. The combination produced greater differences between groups in the decrease in depressive severity (-10.8 vs. -10.1 in olanzapine only, and vs. -9.4 in fluoxetine only, $P < 0.001$ in each instance); a greater response rate (40.4% vs. 25.9%, [$P = 0.003$] and vs. 29.6% [$P = 0.028$], respectively); and a greater remission rate (27.3% vs. 14.7% [$P = 0.003$] and versus 16.7% [$P = 0.012$], respectively).

Synthesis of MDD Outcomes (Tier 1)

To provide information reporting average outcomes in pharmacologic trials of TRD, we calculated weighted means for the change in depressive severity, response rate, and remission rate (Table 32).

Table 32. Mean clinical outcomes for TRD (Tier 1) patients in pharmacologic studies

Clinical Outcome	Switching	Augmentation	Maintenance
Mean change HAM-D	-10.6 (-16.4 to -4.9)	No data	No data
Mean change MADRS	-11.2 (-14.7 to -7.8)	-11.2 (-13.7 to -8.8)	-7.6 (-9.2 to -5.2)
Mean response rates (HAM-D and MADRS)	39.8% (30.7 to 48.9)	38.1% (31.0 to 45.3)	27.3% (19.8 to 34.8)
Mean remission rates (HAM-D and MADRS)	22.3% (16.2 to 28.4)	27.2% (20.4 to 34.0)	16.8% (13.5 to 20.2)

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale
Note: Numbers in parenthesis indicate the 95 percent confidence interval

We quantitatively synthesized weighted means of the changes in depressive severity for studies involving the two interviewer-administered instruments, the HAM-D and MADRS. For patients switched to a new medication, the mean average change in HAM-D was -10.6 points, and the mean average change in studies using the MADRS was -11.2. For patients receiving medication augmentation, the mean change in depressive severity was -11.2 on the MADRS. We also identified seven measures of depressive severity change in patients who continued on their same medication without a change in treatment. Those measured by MADRS showed a mean change of -7.6, with confidence intervals overlapping with switching and augmentation results.

For changes in response rates, results varied greatly, with response rates ranging from 12.1 to 80 percent. The two highest response rates were from a study restricted to an elderly population,[105] a sample distinct from the others. A weighted mean response rate for switch strategies was 39.8 percent. Considering augmentation strategies provided seven more measures, ranging from 11.1 percent to 45.8 percent. A quantitative synthesis of these rates suggests an average response rate of 38.1 percent for TRD patients following an augmentation next-step pharmacologic treatment. For those who maintained on their pharmacologic treatment, we identified five measures of response rates, which ranged from 10 percent to 50 percent. The weighted mean average response rate for maintenance treatment was 27.3 percent.

Finally, for changes in remission rates, we identified measures involving switch strategies that were not restricted to the elderly population. These remission rates ranged from 6.9 percent to 46.7 percent, with a weighted mean average remission rate of 22.3 percent for TRD patients following a switch to a next-step pharmacologic treatment. Five studies with augmentation arms provided five augmentation measures of remission rates, ranging from 15.2 percent to 29.9 percent, with a weighted mean average remission rate of 27.2 percent. For those who maintained

on their pharmacologic treatment, measures of remission showed rates varying from 14.7 percent to 22.4 percent, with a weighted mean average remission rate of 16.8 percent.

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Overview

As with KQ 1, KQ 2 addressed direct or indirect comparisons of the four nonpharmacological interventions (ECT, rTMS, VNS, and either CBT or IPT). Unlike KQ 1, however, we did not include studies that compared pharmacologic interventions. In the detailed analysis section below, first we present the studies by comparison, then by tier, and then by whether the population involves MDD-only patients or an MDD/bipolar mix. Information is presented for the three tiers used in KQ 1 (Tier 1, two or more treatment failures; Tier 2, one or more treatment failures, but not including the studies in Tier 1; and Tier 3, "probable" treatment resistance). Again, only studies with quality ratings of good or fair are featured.

Table 33. Number of studies included by comparison and definition of treatment resistance (tier) for KQ 2

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	2	1
rTMS vs. sham	Tier2: ≥ 1 treatment failure	2 additional	1 additional
rTMS vs. sham	Tier 3: Probable	0	1 additional
ECT vs. rTMS	Tier 3: Probable	1 additional	2 additional
CBT vs. usual care	Tier 3: Probable	1 additional	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; vs. = versus.

We identified a total of 11 studies addressing maintenance of remission using nonpharmacologic interventions (Table 33). Two Tier 1 studies, reported in three articles, compared rTMS versus sham in an MDD-only population, with both indicating that rTMS was superior to sham in preventing relapse.[69,77,99] However, these trials included very few patients in the relapse prevention phase. A third Tier 1 study compared rTMS with sham in an MDD/bipolar mix population. Differences between rTMS and sham were not statistically significant at 1- and 3-months followup.[82]

Tier 2 evidence added three trials comparing rTMS versus sham. Two of these trials involved MDD-only patients (five articles).[86,87,115,116] One study involved an MDD/bipolar mix population.[88] All three trials supported benefit of rTMS over sham in maintaining remission.

Tier 3 evidence added five studies. One study compared rTMS versus sham in an MDD/bipolar mix population, finding benefit again for rTMS over sham.[90] Three studies provided the only head-to-head comparison available, comparing ECT versus rTMS, one in an MDD-only population that was reported in two articles[117,118] and two in an MDD/bipolar mix population that was reported in four articles.[60-63] All studies indicated no difference in maintaining remission at 7 weeks to 6 months followup.

Most studies either allowed patients to continue antidepressants throughout the trial or required that they be given an antidepressant following the active nonpharmacological treatment. The duration of followup for assessing maintenance of remission ranged from 2 weeks to nearly 1 year. The method for assessing maintenance of remission varied among trials. Some trials followed (or randomized) only patients who had achieved a response or remission during active treatment and then measured relapse during a post-treatment period. Other trials followed all

randomized participants during a post-treatment period regardless of response or remission with initial treatment. These trials generally reported the number of patients in remission at the end of treatment and at the end of followup, which provides an indirect measure of maintenance of remission.

Strength of Evidence: Tier 1

There were no Tier 1 direct (head-to-head) comparisons available. The single comparison involving a Tier 1 TRD population was rTMS versus sham; three studies provided insufficient evidence to draw a conclusion (Table 34). Studies found that relapse rates do not differ significantly between rTMS and sham, however, too few patients were followed during the continuation phases of these two studies and patients in the third received a co-intervention, providing insufficient evidence to allow for a conclusion.

Table 34. Strength of Evidence: maintenance of remission of rTMS versus sham – Tier 1

Comparison	Number of studies; subjects*	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
rTMS vs. sham	3; 46	High 3 RCTs Fair	Inconsistent	Indirect	Imprecise	No significant differences in maintenance of remission Insufficient

* Number of subjects reflects only those followed past acute treatment
RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Key Points

Only limited evidence addressed maintenance of remission among MDD patients. These included the following interventions: ECT (2 studies), rTMS (10 studies, including ECT in three head-to-head trials), and CBT (1 study). No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT in patients in a TRD (Tier 1) population. No evidence was identified for VNS. The only evidence for TRD (Tier 1) compared rTMS versus sham.

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

No TRD (Tier 1) data were available for this comparison, but three trials provided direct Tier 3 evidence. One trial in an MDD-only population, reported in two articles, found no statistically significant differences in relapse rates at 3 months and 6 months after treatment ended.[117,118] A second trial in an MDD/bipolar mix population, reported in three articles, provided similar results indicating no statistically significant differences in relapse rates between ECT and rTMS.[61-63] A third trial in an MDD/bipolar mix population reported no statistically significant differences in response and remission rates during a 4-week observation following 3 weeks of acute treatment.[60] However, results of this trial may be confounded by a large number of rTMS patients switching to ECT.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Two Tier 1 MDD-only studies found no statistically significant differences in relapse rates between rTMS and sham at 20 weeks[69] and 6 months.[77,99] A third Tier 1 study, involving an MDD/bipolar mix population, found no statistically significant differences in mean HAM-D scores during acute treatment at 3-month followup.[82] These three studies provided insufficient evidence to draw a conclusion. Studies found that relapse rates do not differ significantly between rTMS and sham, however, too few patients were followed during the continuation phases of two of these studies and patients in the third received a co-intervention, providing insufficient evidence to allow for a conclusion.

Three Tier 2 studies provided data supporting the benefit for rTMS versus sham in maintaining remission. One MDD-only study found greater improvement in symptoms for rTMS patients than for the control patients at 2 weeks post-treatment.[86] Only the high-frequency rTMS delivered to the left dorsolateral prefrontal cortex and the low-frequency rTMS delivered to the right left dorsolateral prefrontal cortex were more effective than the sham intervention. A second study, also in an MDD-only population, found a trend towards lower relapse rates for rTMS compared with sham, but statistically significant differences were not reported.[87,115,116,119] One study involving an MDD/bipolar mix population reported that one patient who responded after rTMS maintained response at 2-month followup.[88]

One Tier 3 study, involving an MDD/bipolar mix population, showed benefit for rTMS versus sham for 3 weeks after treatment ended, but the benefit had disappeared at 3-month followup.[90]

Cognitive Behavioral Therapy Versus Usual Care

No TRD (Tier 1) evidence was available for this comparison. One relatively large study (150 patients) reported in four articles involved a Tier 3, MDD-only population; it supported the benefit of CBT versus usual care in maintaining remission.[95,96,120,121] The initial study compared 20 weeks of CBT with usual care (clinical management involving psychiatrist visits and antidepressant medications) and measured remission rates over a total of 68 weeks. Patients treated with CBT had a lower risk of relapse than sham-treated patients (hazard ratio 0.54; 95% CI, 0.32-0.93; $P = 0.02$). Followup of this population for 6 years after randomization showed small differences in recurrence rates for up to 3.5 years, although actuarial recurrence rates were only statistically significantly different through 20 weeks after randomization.

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD/bipolar mix population.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD/bipolar mix population.

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

In the RCT of ECT versus rTMS,[117,118] 43 participants entered treatment, but only 41 continued in the 6-month followup to assess relapse rates (Table 35). In 20 participants, ECT was delivered according to a protocol with intensity 2.5 times the threshold energy and charge titrated up every second or third treatment to maintain a seizure length of 25 seconds or longer. Twenty-one participants received 20 sessions of high frequency at 90 percent motor threshold and 1,200 pulses per second. Prior to beginning treatment, the mean HAM-D_{17} scores (standard deviation) for patients were 28.4 (9.3) in the ECT group and 25.8 (6.1) in the rTMS group. At the beginning of followup (i.e., end of treatment), mean HAM-D_{17} scores were 7.9 (4.5) in the ECT group and 7.8 (3.7) in the rTMS group. These scores remained relatively stable at 3 and 6 months after treatment ended. At 3 months, 2 of 20 (10%) ECT-treated participants and 1 of 21 (5%) rTMS-treated participants relapsed. At 6 months, the figures were 4 of 20 (20%) and 4 of 21 (19%), respectively. Relapse rates were not statistically significantly different between these groups.

Table 35. Maintenance of remission of ECT versus rTMS: Tier 3, MDD

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Dannon et al., 2002;[117] extension of Grunhaus et al., 2000[118] RCT Fair	**ECT plus antidepressant post-ECT (n = 20)** 35% bilateral, mean sessions = 10.25 (3.1) **rTMS plus antidepressant post-rTMS (n = 21)** High frequency, 20 sessions **Definitions** Response: HAM-D_{17} reduction ≥ 50% and final GAS < 60 Relapse: return of depressive symptoms with HAM-D_{17} ≥ 16 Measured at end of treatment (response) and 3 and 6 months post-treatment (relapse)	**HAM-D_{17}** End of treatment (baseline), mean (SD) ECT: 7.9 (4.5) rTMS: 7.8 (3.7) *P* = NS 3-month post-treatment, mean (SD) ECT: 7.7 (5.0) rTMS: 6.4 (4.9) *P* = NS 6-month post-treatment, mean (SD) ECT: 8.4 (5.6) rTMS: 7.9 (7.1) *P* = NS 3-month relapse, number (%) ECT: 2 (10) rTMS: 1 (5) *P* = NS 6-month relapse, number (%) ECT: 4 (20) rTMS: 4 (19) *P* = NS

ECT = electroconvulsive therapy; GAS = Global Assessment Scale; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item instrument; n = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar

Two additional RCTs compared ECT with rTMS in a mixed population of unipolar and bipolar depression. One RCT compared 6-month remission rates for ECT and rTMS in 46 patients referred for ECT to treat a major depressive episode (Table 36).[61-63] Patients were not required to be treatment resistant, although on average patients had more than two previous treatment failures following adequate courses of medication—mean number (standard deviation) of failed treatments: ECT, 2.5 (1.4); rTMS, 2.4 (1). A small percentage of included participants had diagnoses of bipolar depression (9%) or psychosis (15%). Patients continued their usual medical care and psychotropic medications, with no changes in medication allowed during their active treatment. ECT was administered twice weekly. The number of ECT treatments was based on response, as determined by the referring physicians. High-frequency rTMS was administered for 15 consecutive weekday sessions. At the end of treatment, HAM-D_{17} scores were statistically significantly lower for the ECT group than for the rTMS group ($P = 0.002$), and the ECT group had a greater percentage of patients in remission (59.1% vs. 16.7%, respectively; $P = 0.006$). After 6 months of followup, HAM-D_{17} scores and remission rates were similar for the ECT and rTMS patients.

A second RCT reported 4 weeks of followup after 3 weeks of acute treatment with ECT (n=30) or rTMS (n=30). Patients were not specified to be treatment resistant, but were being referred for ECT for MDD. Most participants had unipolar depression, although 13 percent had bipolar depression. Patients continued their usual medications, with no changes in medication allowed during their active treatment. At the end of 3 weeks of acute treatment, ECT was significantly better than low-frequency rTMS ($P = 0.035$). At the end of 7 weeks (4 additional weeks), response and remission rates were not statistically significantly different for ECT

Table 36. Maintenance of remission of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
McLoughlin et al., 2007[61] Eranti et al., 2007;[62] Knapp et al., 2008[63] RCT Fair	**ECT (n = 22; n = 12 for 6-month followup)** 82% bilateral, mean sessions 6.3 (SD: 2.5) **rTMS (n = 24; n = 4 for 6-month followup)** High frequency, 15 sessions **Treatment strategy** Augmentation **Definitions** Remission: HAM-D_{17} ≤ 8 Response: HAM-D_{17} reduction ≥ 50% Measured at end of treatment and 6 months after baseline (maintenance of remission)	**HAM-D_{17}** Baseline, mean (SD) ECT: 24.8 (5.0) rTMS: 23.9 (7.0) *P* = NS End of treatment, mean (SD) ECT: 10.7 (NR) rTMS: 18.5 (NR) *P* = 0.002 6-month (from baseline), mean (SD) ECT: 13.8 (NR) rTMS: 13.5 (NR) *P* = NS End of treatment remission, n (%) ECT: 13 (59.1) rTMS: 4 (16.7) *P* = 0.006 6-month remission, n (%) ECT: 6 (50) rTMS: 2 (50) *P* = NR
Hansen et al., 2010[60] RCT Fair	**ECT (n = 30)** 100% unilateral, 9 sessions **rTMS (n = 30)** Low frequency, 15 sessions **Treatment strategy** Augmentation **Definitions** Response: HAM-D_{17} reduction ≥ 50% Remission: HAM-D_{17} < 12 Measured at end of treatment (week 3) and after 4 additional weeks (week 7)	**HAM-D_{17}** Baseline, median (range) ECT: 24 (16-34) rTMS: 24 (14-38) *P* = NS Week 3 remission rate (95% CI) ECT: 0.53 (0.34-0.72) rTMS: 0.27 (0.12-0.46) *P* = 0.035 Week 7 remission rate (95% CI) ECT: 0.57 (0.37-0.75) rTMS: 0.40 (0.23-0.59) *P* = 0.200

ECT = electroconvulsive therapy; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item instrument; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

compared with rTMS (*P* = 0.200). Response and remission rates continued to improve for the rTMS group, while no further reduction in HAM-D scores were observed in the ECT group (HAM-D score change from weeks 3–7; *P* = 0.001 and *P* = 0.78, respectively). However, these results are potentially confounded by increases in antidepressant dose and switching from rTMS to ECT during the followup period; 12 of 23 rTMS nonresponders switched to ECT during the 4-week followup.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT in patients in this group. No sham-controlled studies addressed this population for ECT, VNS, or CBT. Two rTMS RCTs using a sham procedure as control addressed maintenance of remission (longer term relapse rates) in an MDD population (Table 37).[69,77,99]

Table 37. Maintenance of remission of rTMS versus sham: Tier 1, MDD

Author, year Design Quality	Intervention and Sample Size Study Details	Results on HAM-D Instruments
Avery et al., 2006[77,99] RCT Fair	**rTMS (n = 35, 11 for relapse followup)** High frequency, 15 sessions over 4 weeks **Sham (n = 33, 2 for relapse followup)** **Treatment strategy** Mixed-within group differences 31% of rTMS group and 27% of control group continued taking medications **Definitions** Remission definition: HAM-D_{21} < 10 Response: HAM-D_{17} reduction ≥ 50% Remission: HAM-D_{17} < 8 Relapse: not defined Measured at end of treatment (visit 16) and reassessed 1 week later (visit 17); Response could enter 6-month followup	**HAM-D_{17}** 6-month relapse, n (%) rTMS: 6 (54.5); 1 lost to followup Sham: 1 (50); 1 lost to followup *P* = NR
Boutros et al., 2002[69] RCT Fair	**rTMS (n = 12, 6 for followup phase)** High frequency, 10 sessions **Sham (n = 9, 1 for followup phase)** **Treatment strategy** Augmentation **Definitions** Response1 definition: >30% decrease in HAM-D_{25} Response2 definition: ≥50% decrease in HAM-D_{25}**calculated from table Relapse: HAM-D_{25} ≥ baseline score ± 10% Relapse measured up until 20 weeks	**HAM-D_{25}** 20-week relapse, n (%) rTMS: 4 (66.6); 1 lost to followup Sham: 1/1 (100) *P* = NS

HAM-D = Hamilton Rating Scale for Depression, 17-item instrument or 25-item instrument; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Subjects in both rTMS trials were allowed to remain on psychotropic medications. The slightly larger and more recently conducted trial (n = 68)[77,99] compared 15 sessions of high-frequency rTMS at 110 percent motor threshold with 1,600 pulses per session with a similarly delivered sham rTMS. At the end of treatment, responders could enter a 6-month followup to assess relapse. The smaller trial (n = 21)[69] compared 10 sessions of high-frequency rTMS at 80 percent motor threshold with 800 pulses per session with a similarly delivered sham rTMS. At the end of treatment responders could enter a 20-week followup.

In both trials, significantly more rTMS-treated than sham-treated participants were classified as responders: respectively, 30.6 percent versus 6.1 percent ($P = 0.008$);[77,99] and 50 percent versus 22 percent ($P < 0.05$)[69]. Of the small number of responders in these trials followed for maintenance of response, more than 50 percent relapsed; no statistically significant differences in relapse rates were observed between the rTMS and sham groups.

MDD/Bipolar

One trial addressed maintenance of remission with rTMS versus sham therapy in a mixed MDD-bipolar population (Table 38).[82] Unlike other studies comparing rTMS and sham stimulation, in this study all patients also received a social support intervention. All patients had treatment failuresof at least two separate trials of a minimum of 4 weeks' duration at therapeutic dosages of antidepressant medications. Two of 48 enrolled patients had bipolar disease; both were randomized to the right rTMS group. Participants were randomized to left- or right-sided delivery of 10 sessions of rTMS or sham and followed for 3 months. At the end of active treatment as well as at 1- and 3-month followup, differences in mean HAM-D scores were not statistically significantly different for rTMS compared with sham. Statistically significant differences were noted between right and left rTMS and right and left sham, consistently showing better reductions for right-sided compared with left-sided delivery ($P = 0.012$). It is possible that the inclusion of a social support intervention may have muffled the effects of rTMS in this study.

Table 38. Maintenance of remission of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Results on HAM-D Instruments
Triggs et al., 2010[82] RCT Fair	**rTMS (n = 16 right(r); n = 18 left(l))** High frequency, 10 sessions over 2 weeks **Sham (n = 14)** **Treatment strategy** Augmentation **Definitions** Response: HAM-D_{24} reduction ≥ 50% Measured at end of treatment and 1 and 3 months after baseline (maintenance of response)	**HAM-D_{24}** End of treatment, mean (SD) rTMS(r): 13.7 (7.6) rTMS(l); 19.8 (9.1) Sham: 17.7 (10.4) *P* = 0.14 1 month, mean (SD) rTMS(r): 11.2 (7.5) rTMS(l); 18.2 (9.8) Sham: 19.7 (11.3) *P* = NS 3 months, mean (SD) rTMS(r): 11.7 (9.3) rTMS(l); 16.3 (11.5) Sham: 17.9 (11.6) *P* = NS

HAM-D24 = Hamilton Depression Scale, 24 item; n = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT. Two trials were relevant for this topic in this patient population (Table 39).

Two RCTs compared rTMS with sham rTMS and assessed maintenance of remission following active treatment.[86,87,115,116] One trial randomized 30 participants to 10 sessions of 3 different rTMS strategies (10 subjects in each group) and 15 participants to 10 sessions of similar sham strategies (5 subjects in each group). The three treatment groups were high frequency delivered to the left dorsolateral prefrontal cortex (left high), low frequency delivered to the left dorsolateral prefrontal cortex (left low), and low frequency delivered to the right left dorsolateral

prefrontal cortex (right low). At the end of treatment, the left high and right low treatment groups had similar reductions in HAM-D_{21} scores, and these differences were statistically significantly greater than the left low and sham groups ($P < 0.001$). These differences remained after 2 weeks of followup; no left low- or sham-treated participants were in remission after 2 weeks, whereas

Table 39. Maintenance of remission of rTMS versus sham: Tier 2, MDD

Author, Year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
Stern et al., 2007[86] RCT Fair	**High rTMS (n = 10)** High frequency, 10 sessions **Low-left rTMS (n = 10)** Low frequency (1 Hz), Left-DLPFC, 10 sessions **Low rTMS (n = 10)** Low frequency,10 sessions **Sham (n = 15)** **Treatment strategy** Switch **Definitions** Remission definition HAM-D_{21} ≤ 10 Response and remission measured at end of treatment (2 weeks) and after 1 and 2 weeks of followup	**HAM-D_{21}** End of treatment score, mean (SD) Left high rTMS: 15.1 (6) Left low rTMS: 27.6 (5.9) Low rTMS: 15.8 (4.8) Sham: 26.7 (3.6) $P < 0.001$ 2-week followup score, mean (SD) Left high rTMS: 13.4 (5.6) Left low rTMS: 26.6 (3) Low rTMS: 14.9 (5.9) Sham: 26.8 (2.3) $P < 0.001$ End of treatment response, n (%) Left high rTMS: 5 (50) Left low rTMS: 0 (0) Low rTMS: 5 (50) Sham: 0 (0%) P = NR 2-week followup response, n (%) Left high rTMS: 4 (40) Left low rTMS: 0 (0) Low rTMS: 6 (60) Sham: 0 (0) P = NR End of treatment remission, n (%) Left high rTMS: 3 (33.3) Left low rTMS: 0 (0) Low rTMS: 1 (10) Sham: 0 (0) P = NR 2-week followup remission, n (%) Left high rTMS: 4 (40) Left low rTMS: 0 (0) Low rTMS: 3 (33.3) Sham: 0 (0) P = NR

Table 39. Maintenance of remission of rTMS versus sham: Tier 2, MDD (continued)

Author, Year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
O'Reardon et al., 2007,[87] Janicak et al., 2007,[115] Solvason et al., 2007[116] Janicak et al., 2010 [119] RCT Fair	**rTMS (n = 99 for followup phase)** High frequency, up to 30 sessions; rescue add-on permitted for symptom breakthrough (deterioration of CGI-S by 1 point over 2-week interval) during continuation **Sham (n = 21 for followup phase)** **Treatment strategy** Acute treatment switch; continuation rescue was augment to current pharmacotherapy **Definitions** Relapse defined as recurrence of the full syndrome of major depression per DSM-IV over ≥ 2 weeks: HAM-D_{17} ≥ 20; CGI-S ≥ 4	**HAM-D_{17} Remission** Score at week 4, mean (SD) rTMS: -14.6 (6.16) Sham: -14.4 (6.11) **Relapse Rates:** Continuation at week 24, n (%) rTMS: 10 (10) Sham: 3 (13.6) *P* = NR

DLPFC = dorsolateral prefrontal cortex; HAM-D = Hamilton Rating Scale for Depression, 21-item instrument; Hz = hertz; MT = motor threshold; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

40 percent of left high- and 33 percent of right low-treated participants were in remission after 2 weeks (*P* = NR).

Another trial followed 120 patients over 24 weeks to assess the durability of acute response to high-frequency rTMS or sham.[87,115,116,119] The acute phase of this trial was a switch strategy that randomized 155 severely depressed participants to active rTMS and 146 severely depressed participants to sham rTMS.[87] After 6 weeks of acute treatment, 44 active rTMS-treated patients and 23 sham rTMS-treated patients were classified as responders. These patients entered a 3-week taper phase, and then began 24 weeks of open-label continuation followup.[115] The remaining nonresponders were offered open-label rTMS, and an additional 32 participants from the original active rTMS group and 49 participants from the original sham rTMS group responded. Of these, durability of response was compared in 99 active rTMS responders and 21 sham responders. Open-label rTMS was permitted as rescue augmentation to the current antidepressant regimen for symptom breakthrough. Relapse was defined as recurrence of the full syndrome of major depression per DSM-IV criteria observed over at least 2 weeks. After 24 weeks, 10 (10%) active rTMS-treated participants relapsed and 3 (13.6%) sham-treated participants relapsed (*P* = NR).

MDD/Bipolar

One RCT compared rTMS with a sham procedure in 20 patients who had at least one adequate pharmacological failed trial during the current or previous episode (Table 40).[88] The majority of included patients (80 percent) had two or more failed medication trials during the current episode. The inclusion criteria allowed patients to have comorbid psychiatric diagnoses provided that the onset occurred after the development of major depression and that the symptoms of major depression were more prominent. This resulted in the inclusion of one patient (assigned to sham) with a bipolar II, depressed diagnosis; the remainder had unipolar major depression. Patients assigned to active treatment (n = 10) received 10 sessions of high-frequency rTMS applied to the left dorsolateral prefrontal cortex. Patients assigned to the sham

intervention (n = 10) received 10 sessions using the same device with the coil angled 30 to 45 degrees off the scalp and the bottom of the coil elevated 0.5 centimeters from the scalp. Response was defined by a 25-item HAM-D score ≤15 and a reduction in this score of 50 percent or more from baseline. At the end of treatment, one rTMS-treated patient (10%) and no sham-treated patients were categorized as responders ($P = 0.09$). The rTMS responder remained a responder during 2 months of followup.

Table 40. Maintenance of remission of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
Berman et al., 2000[88] RCT Fair	**rTMS (n = 10; 1 for followup phase)** High frequency, 10 sessions **Sham (n = 10; 0 for followup phase)** **Treatment strategy** Switch **Definitions** Response: HAM-D_{25} ≤ 15 and reduction from baseline ≥ 50% Response measured at end of treatment (2 weeks) and up to 2 months after treatment	**HAM-D_{25}** End of treatment score, mean (SD) rTMS: 24.6 (NR) Sham: 36.4 (NR) $P < 0.01$ End of treatment response, n (%) rTMS: 1 (10) Sham: 0 (0) $P = 0.09$ 2-month maintained response, n (%) rTMS: 1 (100) Sham: 0 (100) P = NR

HAM-D = Hamilton Rating Scale for Depression, 25-item instrument; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

No trial addressed maintenance of remission with rTMS versus sham therapy in an MDD-only population.

MDD/Bipolar

One RCT compared rTMS with a sham procedure in 19 patients with unspecified drug resistance (Table 41).[90] The majority of patients had unipolar major depression, although 16 percent had bipolar depression. Patients assigned to active treatment (n = 12) received 5 sessions of high-frequency rTMS applied daily to the left prefrontal cortex for 5 days. Patients assigned to the sham intervention (n = 7) received five similar sessions with the coil placed perpendicular to the scalp surface without direct contact. Depression severity was measured by the 24-item HAM-D and the 21-item BDI. At the end of treatment, rTMS-treated patients had significantly lower HAM-D and BDI scores than sham-treated patients ($P < 0.001$). This statistically significant difference was maintained through week 4 (3 weeks after end of treatment), but patients reverted to the previous depressed mood at week 12 (P = NS).

Table 41. Maintenance of remission of rTMS versus sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Bortolomasi et al., 2006 [90] RCT Fair	**rTMS (n = 12)** High frequency, 5 sessions **Sham (n = 7)** **Treatment strategy** Augmentation **Definitions** Outcome = change in HAM-D_{24} and BDI_{21}	**HAM-D_{24}** Baseline score, mean (SD) rTMS: 25.17 (NR) Sham: NR (NR) *P* = NR End of treatment (at week 1), mean (SD) rTMS: 11.33 (NR) Sham: 18.29 (NR) *P* < 0.001 At week 4, mean (SD) rTMS: 11.42 (NR) Sham: 19.14 (NR) *P* < 0.001 At week 12, (NR) Both groups reverted to depressed mood *P* = NS **BDI_{21}** Results similar to HAM-D_{24}

BDI_{21} = Beck Depression Inventory, 21-item instrument; HAM-D_{24} = Hamilton Rating Scale for Depression, 24-item instrument; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Cognitive Behavioral Therapy Versus Usual Care

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with CBT versus usual care in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with CBT versus usual care in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

One trial, lasting 68 weeks and involving 158 participants, compared relapse rates for CBT and sham treatment (Table 42).[95,96,120,121] All participants received usual clinical management and antidepressant drug continuation throughout the study. Participants also were followed for an additional 4.5 years.[121] In the CBT group, 80 participants received 16 sessions over a 20-week period, plus two booster sessions approximately 6 to 14 weeks later. The sham group was seen by a psychiatrist every 4 weeks during the first 20 weeks and then every 8 weeks thereafter. The relapse outcome was defined by two criteria. The first criterion was meeting the criteria from the Diagnostic and Statistical Manual, Version 3, Revised for major depression for 1 month or more, with a HAM-D_{17} score of 17 or higher on two successive visits 1 week apart. The second criterion, which was applied only during the followup phase, was persistent symptoms for 2 months or more with a HAM-D_{17} score of 17 or higher at both visits. At the end of treatment (i.e., 20 weeks) and at 44 weeks, relapse rates were similar between CBT- and sham-treated participants. At the end of 68 weeks, significantly more sham-treated participants than CBT-treated participants had relapsed. Based on the combined definition of major depression with persistent symptoms, 29 percent of CBT-treated participants and 47 percent of sham-treated participants had relapsed by 68 weeks (hazard ratio for relapse 0.54; 95% CI, 0.32-0.93; $P = 0.02$). In a followup study of 135 participants over a total of 6 years, recurrence curves suggested the effects of CBT were persistent for up to 3.5 years, although actuarial recurrence rates were only statistically significantly different through 20 weeks after randomization.[121]

Table 42. Maintenance of remission of CBT versus usual care: Tier 3, MDD

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Paykel et al., 1999[95] Scott et al., 2000;[96] Scott et al., 2003[120] Paykel et al., 2005 [121] RCT Fair	**CBT plus clinical management (n = 80)** 16 session during 20 weeks **Clinical management alone (n = 78)** **Treatment strategy** Augmentation **Definitions** Relapse: HAM-D_{17} ≥ 17 on 2 successive visits 1 week apart, OR, at followup for ≥ 2 months	**Relapse Rates**, number (%) Major depression alone At 20 weeks CBT: 9 (11) Sham: 14 (18) *P* = NR At 44 weeks CBT: 15 (19) Sham: 25 (31) *P* = NR At 68 weeks CBT: 18 (22) Sham: 29 (36) *P* = 0.08 Hazard Ratio: 0.58 (95% CI, 0.37-1.07) **Relapse Rates**, number (%) Major depression plus symptoms At 20 weeks CBT: 8 (10) Sham: 14 (18) *P* = NR At 44 weeks CBT: 19 (24) Sham: 31 (40) *P* = NR At 68 weeks CBT: 23 (29) Sham: 37 (47) *P* = 0.02 Hazard Ratio: 0.54 (95% CI, 0.32-0.93) Recurrence rate in long-term followup At 120 weeks CBT: 27(38) Sham: 28(43) *P* = 0.25 At 275 weeks CBT: 42(60) Sham: 42(65) *P* = 0.33

CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item instrument

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Key Question 3: Efficacy or Effectiveness for Treating Treatment-Resistant Depression for Particular Symptom Subtypes

Overview

This KQ focused on the comparative benefit of treatment for patients with TRD and an accompanying symptom subtype. Specifically of interest were symptom groups such as

psychosis, catatonia, or melancholy, subtypes that can accompany depression and which are often used to inform clinical interventions. We identified no studies that address this question in TRD (Tier 1) patients. However, a consideration of evidence from all tiers identified one relevant Tier 3 trial, reported in two articles.[118,122] The study was a head-to-head comparison of ECT and rTMS in psychotic and nonpsychotic patients with TRD. Though the study was rated poor, we include it here because it provides some evidence on the efficacy of rTMS in patients with TRD and psychosis.

Strength of Evidence: Tier 1 (TRD)

We identified no eligible Tier 1 studies.

Key Points

The one study available on this topic[118,122]was rated poor quality and involved a Tier 3 population with a primary finding that ECT produced significantly better outcomes than rTMS. A secondary analysis indicated that the presence of psychotic symptoms may have influenced the effect of these two interventions: psychotic patients appeared to have better outcomes with ECT than with rTMS. In nonpsychotic patients, the effect of the two interventions was similar. Of note, however, the differential use of psychotropic medications during the course of the trial may have biased the results in favor of ECT. The two groups were being treated with different drugs at baseline; ECT patients were allowed to continue any medication, including antipsychotics, at a stable rate, but the rTMS patients were limited to clonazepam.

Detailed Analysis

ECT Versus rTMS

There were no eligible studies in Tier 1 or 2. In Tier 3, there were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies in an MDD-only population and one study (two articles) in an MDD/bipolar mix population.

MDD-Only

There were no eligible studies.

MDD/Bipolar Mix

The study was undertaken with 40 inpatients and outpatients who had been referred for ECT; detailed information is available in the evidence table in Appendix D. The investigators randomized patients to either ECT or rTMS. Of those receiving ECT, 10 had TRD only and 10

had TRD and psychosis; of those receiving rTMS, 11 had TRD only and 9 had TRD and psychosis. The primary comparison was the change in HAM-D score at 2 weeks and end of treatment (approximately 4 weeks), with higher scores better than lower scores.

Overall, patients responded better to ECT than to rTMS ($P < 0.05$). With regard to psychotic versus nonpsychotic patients, the study reported two important findings. First, in nonpsychotic patients, ECT and rTMS were equally effective. HAM-D_{17} scores at the end of treatment for ECT and rTMS were 13.9 and 11.0 (P = NS), respectively. Second, in psychotic patients, ECT appeared to be more effective than rTMS; HAM-D_{17} scores at the end of treatment were 8.4 and 20.8 ($P = 0.01$), respectively.

This study has limitations for our KQ because treatment bias restricted applicability to our population of interest. The ECT group had been allowed to continue on any psychotropic medication, including antipsychotic medications, at a stable dose, while the rTMS group had all their psychotropic medications discontinued although they were prescribed clonazepam (a benzodiazepine derivative with anticonvulsant, muscle relaxant, and anxiolytic properties) to reduce anxiety, limit insomnia, and help prevent seizures. This variation introduced a treatment, or co-intervention, bias. In this sample, 25 patients had been treated unsuccessfully 2 or more times and 15 patients either had been treated unsuccessfully only one time or had had no treatment failures; nonetheless, all had been referred for ECT, and so we classified them as Tier 3 (probable treatment resistance).

Key Question 4: Organization of Safety, Adverse Events, and Adherence

KQ 4 contains information addressing safety, adverse events, and adherence in the use of nonpharmacological treatments to treat TRD. The following section is split into four segments, each comparing the effects of the four nonpharmacologic interventions (ECT, rTMS, VNS, CBT/IPT) with each other (head-to-head comparisons) or with control interventions (e.g., sham procedures) but focusing on a different outcome. KQ 4a addresses the impact on cognitive functioning. KQ 4b examines specific adverse events (other than cognitive functioning) that were assessed systematically. The next two segments use two measures of study withdrawals. KQ 4c examines general tolerability to the treatments by using withdrawals specifically due to adverse events. The final segment, KQ 4d, examines adherence by examining withdrawals for any reason (overall withdrawals), as only a few studies measured adherence as an outcome.

Key Question 4a: Cognitive Functioning—Overview

This KQ concerns the issue of whether the four nonpharmacologic interventions (ECT, rTMS, VNS, CBT/IPT) compared with each other (head-to-head comparisons) or against control interventions (e.g., sham procedures) have different effects on cognitive functioning. Cognitive functioning is measured in several domains, such as the Mini-Mental Status Examination (MMSE) and various intelligence, learning, or memory tests such as the Rey Auditory Verbal Learning Test (RAVLT), the Wechsler Adult Intelligence Scale (WAIS), and the Cambridge Examination for Mental Disorders of the Elderly (and the cognitive, self-contained part of the Cambridge instrument denoted CAMCOG). Appendix F lists the major instruments used to detect or diagnose cognitive impairments across a wide range of faculties.

We included 11 studies of either good or fair quality; of these, 5 compared ECT to rTMS, 5 evaluated rTMS against a sham procedure, and one compared ECT to ECT plus rTMS (Table 43). Only one had cognitive functioning as a primary outcome of interest. All tested cognitive functioning effects in the acute phase of treatment and did not address long-term or cumulative effects of the interventions. In the detailed analysis section below, we consider first the studies involving only patients with MDD and then the mixed MDD/bipolar populations. For studies that did not report sufficient information to determine if the population was MDD-only or a mixed MDD/bipolar population, we placed them in the mixed MDD/bipolar section. Information is presented for the three tiers used throughout this report: Tier 1, two or more treatment failures; Tier 2, one or more treatment failures; and Tier 3, "probable" treatment resistance.

Table 43. Number of good- and fair-quality studies by TRD tier and diagnostic mix for KQ 4a

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	2	0
ECT vs. rTMS	Tier 2: ≥ 1 treatment failure	1	0
ECT vs. rTMS	Tier 3: Probable	0	2 additional
ECT vs. ECT + rTMS	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	3	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2 additional	0

ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation, vs. = versus

When considering only studies conducted in Tier 1 patients with MDD, there were two head-to-head trials of ECT versus rTMS,[58,123] one trial comparing ECT to ECT plus rTMS,[64] and three rTMS versus sham studies (four articles).[73,76,77,99]

Additional eligible studies were found in Tiers 2 and 3. One head to head study was conducted in Tier 2 patients and compared ECT to rTMS.[59] Two studies (six articles) comparing rTMS to sham were conducted in Tier 2 patients with MDD.[84,85,87,115,116,119,124,125] Two head-to-head studies (four articles) in Tier 3 compared ECT with rTMS.[61-63,126]

Strength of Evidence: Tier 1 (TRD)

Table 44 shows the evidence for studies limited to Tier 1, patients that have two or more previous treatment failures for depression. The two studies that compare ECT versus rTMS, one an RCT and the other a cohort study, provide insufficient evidence to determine whether there is a difference in cognitive outcomes between ECT and rTMS during the acute phase of treatment. In the three studies that populate Tier 1 on comparisons of rTMS versus sham, there is insufficient evidence to assess the impact of rTMS on cognitive functioning during acute phase treatment.

Table 44. Strength of Evidence: impact on cognitive functioning – Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results Strength of Evidence
ECT vs. rTMS	2; 72	Medium 1 RCT, and 1 prospective cohort study Both fair	Inconsistent	Direct	Imprecise	Some evidence suggests no difference between treatments, whereas some evidence suggests that ECT has a deleterious impact on cognitive functioning compared to rTMS Insufficient
ECT vs. ECT plus rTMS	1;22	High 1 RCT Fair	Unknown	Indirect	Imprecise	Insufficient
rTMS vs. sham	3; 101	Medium 3 RCTs, 1 good, 2 fair	Inconsistent	Indirect	Imprecise	Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham Insufficient

ECT = electroconvulsive therapy; RCT(s) = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 4a: Cognitive Functioning—Key Points

Limited evidence addressed the impact of these procedures on cognitive functioning; no evidence was available for VNS or CBT/IPT.

Overall, we included 11 studies (20 articles) that examined cognitive functioning during acute phase treatment.[58,59,61-64,73,76,77,84,85,87,99,115,116,119,123-126] Nine studies were limited to patients with MDD-only, 4 comparing ECT with rTMS,[58,59,123,126] and 5 studies (12 articles) comparing rTMS with sham.[73,76,77,84,85,87,99,115,116,119,124,125] Two studies (five articles) included a mixed (20 percent or less bipolar) population; one study (three articles) compared ECT with rTMS,[61-63] and the second study compared ECT versus ECT plus rTMS.[64]

Included studies are mostly small; samples had a mean of 35 participants per study and ranged from 15[76] to 68[77,99] participants per study with the exception of one study that had 325 participants.[87,115,116,119,124,125] Overall, cognitive functioning impacts did not differ much between treatment groups. Some tests did show a statistically significant difference but not necessarily a clinically meaningful one.[73,76,77,84,85,99]

Any negative cognitive functioning impact that did occur with ECT faded away relatively quickly. Differences tended to dissipate to insignificance between end of treatment assessments and subsequent assessments (mean 8.8 days,[126] 2 weeks,[126] and 6 months[61-63]).

Key Question 4a: Cognitive Functioning—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation

There were two studies, an RCT and a prospective cohort study, in Tier 1. There was one study in Tier 2. In Tier 3, there was one RCT and one prospective cohort study.

Tier 1

There were two studies, an RCT and a prospective cohort study.

MDD-Only

Two studies, shown in Table 45, provided data on the head-to-head comparison of ECT versus rTMS.[58,123] One was an RCT that compared right unilateral ECT for 2 weeks in 20 patients with high-frequency rTMS in 22 patients.[58] At the end of treatment at 2 weeks and after a 2-week followup, for a total of 4 weeks, the groups did not differ on cognitive tests that included the Weschler Adult Intelligence Scale, Weschler Memory Scale, and the Rivermead Behavioral Memory Test.

The other was a prospective cohort study of 30 subjects.[123] The study used RAVLT, Memory for Persons Test, Autobiographical Memory Interview, Four card task, and the Squire Subjective Memory Questionnaire (SSMQ) to test cognitive functioning. Several of the cognitive tests showed a statistically significant difference between the ECT and rTMS groups, with ECT having a deleterious effect on cognitive functioning compared to rTMS. Two sections of the RAVLT showed significant differences in post-treatment measures in favor of rTMS: recall after interference (ECT 3.9 vs. rTMS 1.8; $P < 0.01$), recall after delay (ECT 4.2 vs. rTMS 2.4; $P < 0.05$). Differences were also found in retrograde memory function. The ECT group made significantly more errors than those in the rTMS group in recognizing words learned before treatment (ECT 5.0 vs. rTMS 1.1, $P = 0.025$). After treatment, ECT recipients also recalled significantly fewer items (0.4) from the visual card task administered before treatment than did the rTMS group (1.4, $P = 0.012$). Subjective memory, measured using the SSMQ, improved in the rTMS group from -16.8 to 3.8 and stayed similar in the ECT subjects, changing from -20.7 to -15.2 at endpoint ($P < 0.05$ for rTMS vs. ECT).

MDD/Bipolar mix

There were no eligible studies.

Tier 2

One fair rated RCT comparing rTMS to ECT in 40 MDD only patients is presented in Table 46.[59] There were no differences in cognitive functioning as measured by the MMSE.

Table 45. Impact on cognitive functioning of ECT versus rTMS: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Rosa et al, 2006[58] RCT Primary endpoint was after up to 4 weeks of active treatment Fair	**ECT (n = 20)** % bilateral NR, mean sessions 10 (SD 1.5) **rTMS (n = 22)** High frequency, 10-20 sessions (2-4 weeks)	**WAIS-R, subsections of WMS (digit span) and RBMT**;: ECT vs. rTMS: no significant differences

Table 45. Impact on cognitive functioning of ECT versus rTMS: Tier 1, MDD (continued)

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Schulze-Rauschenbach et al., 2005[123] Prospective cohort Outcomes measured 8.8 days on average after last treatment Fair	**ECT (n = 14)** Right unilateral txt for 2 weeks **rTMS (n = 16)** High frequency, mean 10.8 sessions (SD 1.4)	**Learning and Anterograde Memory with AVLT:** Recall after interference: Before treatment ECT: 2.8 (2.2) vs. rTMS: 3.2 (1.9) 1 week after treatment ECT: 3.9 (1.9) vs. rTMS: 1.8 (2.0), *P* < 0.01 Recall after delay: Before treatment ECT: 2.4 (1.8) vs. rTMS: 3.2 (1.6) 1 week after treatment ECT: 4.2 (1.6) vs. rTMS: 2.4 (2.0), *P* < 0.05 Other AVLT subscales or the Memory for Persons Test (MPT): No significant differences Retrograde memory with AVLT Recall: No difference on recall or recognition hits Recognition false alarms 1 week after treatment: ECT: 5.0 (3.0) vs. rTMS: 1.1 (1.1), *P* < 0.05 Four-card task - Free recall: 1 week after treatment ECT: 0.4 (0.5) vs. rTMS: 1.4 (1.2), *P* < 0.05 **Subjective memory with SSMQ***:* Before treatment ECT: -20.7 (19.0) vs. rTMS: -16.8 (16.9) 1 week after treatment ECT: -15.2 (25.2) vs. rTMS: 3.8 (11.8), *P* < 0.05

AVLT = Auditory Verbal Learning Test; ECT = electroconvulsive therapy; MPT = memory persons test; n = number; NR = not reported; pt = patient; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SSMQ = Squire Subjective Memory Questionnaire; txt = treatment; vs. = versus; WAIS-R = Weschler Adult Intelligence Scale-Revised; WMS = Weschler Memory Scale

Table 46. Impact on cognitive functioning of ECT versus rTMS: Tier 2, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Grunhaus et al., 2003[59] RCT 2-4 weeks Fair	**ECT (n = 20)** 35% bilateral, mean sessions 10.25 (SD 3.1) **rTMS (n = 20)** High frequency, 20 sessions (4 weeks)	**MMSE** Baseline (SD) ECT: 25.8 (3.4) rTMS: 27.8 (3.0) Week 2 (SD) ECT: 26.3 (2.9) rTMS: 27.8 (3.0) End of treatment (SD) ECT: 27.1 (2.5) rTMS: 28.0 (1.8) Group by time interaction, *P* = NS

ECT = electroconvulsive therapy; NS = not significant; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; vs. = versus

Tier 3

There were no MDD studies and in an MDD/bipolar mix there was one RCT and one prospective cohort study (Table 47).

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One RCT and one prospective cohort study provide head-to-head evidence comparing rTMS with ECT for mixed MDD/bipolar populations, as shown in Table 47.[61-63,126] The RCT compared high-frequency rTMS (n = 22, for 15 sessions) versus ECT (n = 24, mean number of sessions 6.3, range 2-10, based on physicians' opinion).[61-63] The primary cognitive tests included the MMSE and CAMCOG. There were no statistically significant differences in MMSE scores or total CAMCOG scores between the ECT group and the rTMS group. In addition, most of the CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory) showed no significant differences; but subjects treated with ECT did statistically significantly better than those treated with rTMS on the attention and orientation subscale (respectively, an increase of 1.1 from baseline versus a decline of 1.2 from baseline; $P = 0.004$).

Table 47. Impact on cognitive functioning of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Quality	Intervention and Sample Size Study Details	Outcomes
McLoughlin et al., 2007[61] Eranti et al., 2007[62] and Knapp et al., 2008[63] RCT Primary endpoint is end of treatment (at clinicians' discretion for ECT group, 3 weeks in rTMS) Good	**ECT (n = 24)** 82% bilateral **rTMS (n = 22)** High frequency, 15 sessions	**CAMCOG attention and orientation subscale** (max = 17), n (SD). Baseline ECT: 12.8 (3.2) rTMS: 14.7 (3.0) End of treatment ECT: 13.9 (3.6) rTMS: 13.5 (3.3) 6 mos ECT: 13.9 (3.5) rTMS: 13.4 (3.8) *P* = 0.004 CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory): No significant differences **MMSE** Baseline, n ECT: 16 rTMS: 22 Baseline, mean (SD) ECT: 24.3(3.6) rTMS: 25.7 (3.9) End of treatment/6-month followup, mean (SD) ECT: 25.6 (3.9)/25.4 (5.3) rTMS: 24.4 (5.3)/24.7 (4.8) Change at end of treatment, mean: ECT: 1.3 rTMS: -1.3 *P* < 0.08 **Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects**: No significant differences on the self-reported cognitive side effects.

Table 47. Impact on cognitive functioning of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder (continued)

Author, Year Design Quality	Intervention and Sample Size Study Details	Outcomes
O'Connor et al., 2003[126] Prospective cohort Outcomes recorded at end of treatment and after 2 weeks of followup Fair	**ECT (n = 14)** unilateral, 3 times per week for 2 to 3 weeks **rTMS (n = 14)** high frequency, 10 sessions	**RAVLT, Acquisition**, mean (SD). Baseline ECT 43.78 (11.07) rTMS 43.71 (12.09). End of treatment ECT 29.14 (7.93) rTMS 43.00 (10.09) *P* < 0.01 2 weeks later: ECT 46.92 (10.80) rTMS 44.07 (10.43) *P* > 0.05. **RAVLT, Retention** (15-item word list after a 20-minute delay interval), mean (SD) Baseline: ECT 8.07 (4.49) rTMS 9.76 (3.08) End of treatment: ECT 2.14 (1.99) rTMS 8.23 (2.80) 2 weeks later ECT 8.92 (4.14) rTMS 8.31 (4.07). **TNET** Baseline: ECT 64.30 (19.40) rTMS 55.63 (18.12). End of treatment: ECT 39.10 (13.21) rTMS 57.81(18.33) 2 weeks later: ECT 59.20 (20.67) rTMS 61.54 (19.12).

CAMCOG = Cambridge Examination for Mental Disorders in the Elderly; ECT = electroconvulsive therapy; MMSE = mini-mental state examination; mos = months; MT = motor threshold; n = number; NR = not reported; pps = pulses per second; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; Rtms = repetitive transcranial magnetic stimulation

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Within Tier 1, there was one RCT identified in an MDD patient population.

Tier 1

One RCT was conducted in 22 MDD patients (Table 48).[64] Memory problems, as measured by a single self-report question, were reported by twice as many patients in the ECT only group (*P* = NS).

Table 48. Impact on cognitive functioning of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Pridmore et al., 2000[64] RCT Outcomes measured after 2 weeks Fair	**ECT (n = 11)** 100% unilateral, 6 sessions **ECT plus rTMS (n = 11)** ECT: 100% unilateral (day 1), plus high frequency rTMS: (days 2-5) Repeated in week 2, 8 sessions	**Memory complaints, n** ECT: 9 ECT plus rTMS:.4 *P* = NS

ECT = electroconvulsive therapy; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

rTMS Versus Sham

Within Tier 1, three RCTs were identified in an MDD patient population, and no eligible studies in an MDD/bipolar mix population were identified. Two additional RCTs in an MDD patient population was identified when accounting for a Tier 2 definition. For MDD/bipolar patients, there were no eligible studies in Tier 2. Within Tier 3 in an MDD-only population, there were no eligible studies.

Tier 1

There were three RCTs in MDD patients and one RCT in patients with MDD/bipolar mix (Table 49).

MDD-Only

Three Tier 1 RCTs as shown in Table 49 evaluated rTMS against sham. The largest (n = 68) used high-frequency rTMS for 15 sessions and took cognitive measurements at baseline and following the final treatment. None of the tests showed a statistically significant difference between the two groups.[77,99] The other two studies were smaller. One (n = 15) used high-frequency rTMS for ten sessions.[76] Tests included the RAVLT, Digit Symbol Test, Digit Span, and Stroop Test. Subjects in the two groups performed equally well with the exception of one measure of verbal memory, Trial 7 of RAVLT, in which subjects who received rTMS performed slightly better (12.7) than sham subjects (12.0, $P < 0.05$). Subjects treated with rTMS had mean neuropsychological tests that were either improved or equal to baseline levels of functioning. The other (n = 18) randomized subjects to five sessions of high-frequency rTMS, low frequency rTMS, or sham.[73] Between-group differences in changes in verbal memory performance were identified (Date NR, group by time interaction $P = 0.006$). The high-rTMS group showed improvement, the sham group showed deterioration, and the sham group showed no change in learning performance.

MDD/Bipolar mix

No eligible studies identified.

Table 49. Impact on cognitive functioning of rTMS versus sham: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Avery et al., 2006[77,99] RCT Outcomes measured after 2 weeks (except GOAT) Good	**rTMS (n = 35)** High frequency, 15 sessions over 4 weeks **Sham (n = 33)**	**RAVLT, Digit Symbol Test and Digit Span (from the WAIS-R), Trail Making Test Parts A and B, MMSE, COWAT, the color Stroop Test: or GOAT**, 5 minutes after each rTMS session: No significant differences -
Holtzheimer et al., 2004[76] RCT Outcomes measured after 2 weeks Fair	**rTMS (n = 7)** High frequency, 10 sessions **Sham (n = 8)**	**Verbal Memory** RAVLT, Trial 7, mean score (%): rTMS: 12.7 (2.1) Sham: 12.0 (2.3), $P < 0.05$. **Neuropsychological measures of attention, verbal memory, psychomotor speed, and mental flexibility. Outcome measures: RAVLT subscales, Digit Symbol Test, Digit Span, and the Stroop Test:** No significant differences
Padberg et al., 1999[73] RCT Outcomes measured after 1 week Fair	**rTMS (n = 6)** High frequency, 5 sessions **Low-left rTMS (n = 6)** 0.3 Hz, Left-DLPFC, 5 sessions **Sham (n = 6)**	**Verbal memory performance** Data NR Group by time interaction $P = 0.006$

COWAT = Controlled Oral Word Association Test; GOAT = Galveston Orientation and Amnesia Test; MMSE = mini-mental state examination; n = number; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; WAIS-R = Weschler Adult Intelligence Scale-Revised

Tier 2

There were two RCTs in MDD patient populations. Within an MDD/bipolar population there were no eligible studies (Table 50).

MDD-Only

One RCT (n = 20) (two articles) compared high-frequency rTMS intervals, for five sessions, with a sham procedure (see Table 50).[84,85] Cognitive testing was completed at baseline and 3 days after the last (fifth) treatment. The rTMS group showed a significant improvement in Trail Making Test B test scores (baseline score: 87.22; endpoint: 58.59; $P < 0.05$), whereas scores for the sham group did not significantly change. The groups did not differ significantly on any other cognitive tests conducted (MMSE, Trail Making Test A, The Stroop Test, WAIS-R Digit Symbol; Controlled Oral Word Association Test, Boston Naming Test, Sentence Repetition, RAVLT, or Judgment of Line Orientation).

The second RCT (n = 325) compared high-frequency rTMS intervals, at 6 weeks, with a sham procedure (see Table 50).[87,115,116,119,124,125] Cognitive testing was completed at baseline and at 6 weeks. The groups did not differ significantly on any of the cognitive tests conducted, which included the MMSE, the Buschke Selective Reminding Test, and the Autobiographical Memory Interview, nor were there significant changes within the groups from baseline to endpoint at 6 weeks.

Table 50. Impact on cognitive functioning for rTMS versus sham: Tier 2, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
O'Reardon et al., 2007;[87] Janicak, 2007;[115] Sovason et al., 2007;[116] Janicak et al., 2010[119] Demitrack et al., 2009;[124] Janicak et al., 2008[125] RCT Outcomes measured at 6 weeks Good	**rTMS (n = 165)** High frequency,, 20-30 sessions **Sham (n = 160)**	**MMSE** Baseline (SD) rTMS: 28.5 (1.5) Sham: 28.4 (1.7) At 6 weeks- end of acute treatment (SD) rTMS: 28.8 (1.4) Sham: 28.4 (1.8) *P* = NS **Short-term recall – BSRT** Baseline (SD) rTMS: 47.6 (12.3) Sham: 47.4 (13.3) At 6 weeks- end of acute treatment (SD) rTMS: 49.4 (12.3) Sham: 49.1 (12.9) *P* = NS **Amnesia Scores (AMI – Short Form)** At 6 weeks – end of acute treatment (SD) rTMS: 88.5 (8.7) Sham: 89.8 (8.1) *P* = NS
Manes et al., 2001[84] and Moser et al., 2002[85] RCT Outcomes measured a mean of 3 days following 1 week treatment Fair	**rTMS (n = 10)** High Frequency 5 sessions **Sham (n = 10)**	**MMSE, Trail Making Test A, The Stroop Test, WAIS-R Digit Symbol; COWAT, Boston Naming Test, Sentence Repetition, RAVLT** (% of learned words recalled after delay), **Judgment of Line Orientation**: No significant differences **Trail Making Test B, seconds** Baseline rTMS: 87.22 Sham: 103.67 Mean of 3 days after end of treatment rTMS: 58.59 Sham: 100.64 *P* < 0.05

AMI = Autobiographical Memory Interview; COWA = Controlled Oral Word Association; MMSE = mini-mental state examination; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; WAIS-R = Wechsler Adult Intelligence Scale-Revised

MDD/Bipolar mix

There were no eligible studies.

Tier 3

In MDD-only and MDD/bipolar populations there were no eligible studies.

Key Question 4b: Specific Adverse Events—Overview

This part of KQ 4 concerns specific adverse events from one of the procedural interventions recorded using a systematic method. Results are presented for good- or fair-quality studies.

Overall, 8 studies (16 articles) presented in Table 51[61-64,77,83,87-89,98,99,115,116,119,124,125] assessed adverse events during acute phase treatment using a systematic method of which only 3 studies (4 articles) found any significant differences in adverse events.[77,88,89,99]

Table 51. Number of good- and fair-quality studies by TRD tier and diagnostic mix that measure adverse events systematically for KQ 4b

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 3: Probable	0	1 additional
ECT vs. ECT+rTMS	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2 additional	2 additional
VNS vs. sham	Tier 1: ≥ 2 treatment failures	0	1

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Strength of Evidence: Tier 1 (TRD)

Table 52 documents the strength of evidence concerning specific adverse events in both disease categories combined, limited to Tier 1 studies. It included three comparisons, one of ECT versus ECT plus rTMS,[64] another study (two articles) that compares rTMS to sham[77,99] and one that compares VNS to sham.[98] The comparison of ECT with ECT plus rTMS found no differences. These studies provide low strength of evidence that both rTMS and VNS compared to sham lead to a greater incidence of adverse events. This low strength of evidence is subject to change with the addition of more studies.

One RCT comparing VNS with sham provided low strength of evidence that there were no significant differences overall in the systematic assessment of specific adverse events, although the reporting of particular events appears to be numerically higher in the VNS group.

Key Question 4b: Specific Adverse Events—Key Points

Evidence on adverse events is very limited; only 8 studies (16 articles)[61-64,77,83,87-89,98,99,115,116,119,124,125] reported specific adverse events using a systematic method; 4 of these found some differences in adverse events.[77,88,89,98,99] This section does not include studies assessing cognitive function; those are addressed in KQ 4a. The single good-quality RCT, a head-to-head comparison of ECT versus rTMS, did not report any significant differences in specific adverse events.[61-63] Five of the studies compared rTMS versus sham procedures; of these, one used escitalopram (20 mg) in both groups. These five studies provide some evidence that rTMS results in more scalp pain and discomfort at the stimulation site, toothache, and muscle twitching than sham, but that there is no difference in headaches or seizures and the adverse effects tend to fade rapidly.

Table 52. Strength of Evidence: specific adverse events – Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. ECT plus rTMS	1; 22	High 1 RCT Fair	Unknown, single study	Indirect	Imprecise	No significant differences in specific adverse events Low
rTMS vs. sham	1; 68	High 1 RCT Good	Unknown, single study (as most of the specific adverse events were assessed by a single study)	Indirect	Imprecise	Some evidence suggests no significant differences in specific adverse events, while some evidence suggests that rTMS results in more scalp pain at the stimulation site Low
VNS vs. sham	1; 235	Medium 1 RCT Fair	Unknown, single study	Indirect	Imprecise	Some differences in specific adverse events reported but *P* = NR Low

CBT = cognitive behavioral; ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation, VSN = vagus nerve stimulation

One RCT comparing VNS with sham did not test the statistical significance of differences in specific adverse events. This study did report an increased frequency of particular events with VNS treatment—including voice alteration, cough, dyspnea, dysphasia, and neck pain.

Key Question 4b: Specific Adverse Events—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

There were no eligible studies in Tier 1 or 2. In Tier 3 there were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Table 53 shows one head-to-head RCT that compared ECT (n = 24) with rTMS (n = 22) and did not report any significant differences in specific adverse events.[61-63] The study used the Columbia ECT Subjective Side Effects Schedule, modified to include potential rTMS side effects (e.g., seizure induction, scalp discomfort, hearing loss) and any upredictable side effects. The study reported that the ECT group had lower overall scores for subjective side effect symptoms at the end of treatment (P = 0.02), but did not find differences in the group by time interaction analysis (P = 0.49). The study did not report frequency of each specific side effects. Additionally there was one death in the rTMS arm; however, it was unrelated to treatment.

Table 53. Adverse events assessed systematically of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome Scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
McLoughlin et al., 2007,61 Eranti et al., 2007,62 and Knapp et al., 200863 RCT ECT CSSES modified Good	**ECT (n = 24)** 82% bilateral, mean session 6.3 (2.5) **rTMS (n = 22)** High frequency, 15 sessions	**CSSES** Baseline mean (SD) ECT: 14.2 (4.7) rTMS 13.2 (5.8) End of Treatment ECT: 6.7 (6.4) rTMS: 9.7 (4.6) At 6 months ECT: 7.1 (4.7) rTMS: 8.9 (4.7) Group effect P = 0.02 Group by time interaction, P = 0.49 No treatment-related major adverse events recorded during study (i.e., seizure induction, anesthetic complications, mania)

CCSES = Columbia Subjective Side Effects Schedule; ECT = electroconvulsive therapy; P = p-value; RCT = randomized controlled trial; rTMS = repetitive thranscranial magnetic stimulation

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

There were no eligible studies in Tier 2 or 3. In Tier 1, there was one eligible study in an MDD-only population and zero studies in an MDD/bipolar mix population.

Tier 1

There one study in an MDD-only population and no studies in an MDD/bipolar mix population.

Table 54 shows one study that compares ECT in 11 patients to ECT plus rTMS in another 11 patients.[64] The ECT-only arm had more side effects numerically (P = NR) than the mixed arm, while differences between groups on specific side effects were not significant. The authors attribute the difference to the reduction in ECT treatments in the mixed group that had some rTMS instead of ECT.

Table 54. Adverse events assessed systematically of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Design Outcome Scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Pridmore et al., 2000[64] RCT A six-item self-report side-effects questionnaire Fair	**ECT (n = 11)** 100% unilateral, 6 sessions **ECT plus rTMS (n = 11)** ECT: 100% unilateral (day 1), plus high frequency rTMS: (days 2-5) Repeated in week 2	**Positive side-effects questionnaire score** ECT: 56 ECT plus rTMS: 31. *P* = NR Patients reporting side effects at week 2 Headache ECT: 9 ECT plus rTMS: 6 Muscle Pains ECT: 6 ECT plus rTMS: 4 Breathing problems, other pains, other problems (Data NR) For all comparisons, *P* = NS

CCSES = Columbia Subjective Side Effects Schedule; ECT = electroconvulsive therapy; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive thranscranial magnetic stimulation

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1 consists of one RCT in patients with a diagnosis of MDD and no studies in patients with a mixed diagnosis of MDD/bipolar. In Tier 2 there were no eligible studies in the MDD-only population and two RCTs in an MDD/bipolar population. Within Tier 3, no eligible studies were identified.

Tier 1

There was one RCT in patients with a diagnosis of MDD and no studies in patients with a mixed diagnosis of MDD/bipolar.

MDD-Only

One RCT (N = 68) comparing high-frequency rTMS to sham used the SAFTEE (Systematic Assessment for Treatment Emergent Effects) instrument to measure adverse events, as seen in Table 55.[77,99] The results showed no significant differences between rTMS and sham. Additionally it was reported that zero seizures occurred in subjects in both groups. However, the rTMS group experienced more occasions of scalp pain at the stimulation site at session one (41 percent) and session 15 (33 percent) than the sham group (0 and 3 percent, respectively).

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were two studies in the MDD-only population and two RCTs in an MDD/bipolar population.

Table 55. Adverse events assessed systematically of rTMS versus sham: Tier 1, MDD

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Avery et al., 2006[77,99] RCT SAFTEE Scores Good	**rTMS (n = 35)** High frequency, 15 sessions over 4 weeks **Sham (n = 33)**	**SAFTEE Scores** Scalp pain at the stimulation site,% Session 1: rTMS: 41 vs. sham: 0, *P* < 0.05 Session 15: rTMS: 33 vs. sham: 3, *P* < 0.05 Seizures, n: rTMS: 0 vs. sham: 0 Changes in SAFTEE (from baseline in 128 individual scores for any emerging symptoms that suggest adverse effects): rTMS vs. sham *P* = NS (Data = NR)

N = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SAFTEE = Systematic Assessment for Treatment Emergent Effects

MDD-Only

Table 56 contains the two studies that compare rTMS to sham.[83,87,115,116,119,124,125] The first study used a modification of the Medical Dictionary for Regulatory Activities (MedRA) to code spontaneously reported adverse events. Adverse events recorded include headache, discomfort at stimulation site, insomnia, worsening of depression or anxiety, gastrointestinal, fatigue, muscle aches, vertigo, facial muscle twitching, and other. There were no statistical differences between rTMS and sham in the adverse events recorded.

The second study, as seen in Table 56, also used MedRA to record spontaneously reported adverse events. The following events occurred at a rate greater than 5 percent and occurred at least twice as much in the rTMS patients than sham: eye pain, toothache, application site discomfort, application site pain, facial pain, muscle twitching, and pain of skin. There were no statistical differences reported (*P* = NR).

MDD/Bipolar mix

Table 57 shows the two studies that compare rTMS to sham in Tier 2 patients diagnosed with MDD and bipolar disorder. One RCT reported no difference in trouble concentrating between rTMS and sham groups.[88] This study also compared adverse events using a multiple-symptom "Side Effect Checklist." Adverse events recorded include poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appetite, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor coordination, and muscle stiffness. Only one adverse event showed a significant difference between comparisons. "Difficulty starting urination" was reported significantly more often among the rTMS patients (2.0 vs. 1.1, *P* = 0.03) (Table 57).[88]

Table 56. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events
George et al., 2010[83] RCT MedRA used Good	**rTMS (n = 92)** High frequency, 15 sessions **Sham (n = 98)**	**Med RA** Headache, discomfort at stimulation site, insomnia, worsening of depression or anxiety, gastrointestinal, fatigue, muscle aches, vertigo, facial muscle twitching, and other: No significant difference
O'Reardon et al., 2007,[87] Janicak, 2007*;[115] Solvason et al, 2007;[116] Janicak et al., 2010;[119] Demitrack et al., 2008[124] Janicak et al., 2008[125] RCT MedRA used Fair	**rTMS (n = 165)** High frequency, 20-30 sessions **Sham (n = 160)**	**MedRA** Exacerbation of depression, % rTMS:0.6 vs. sham:1.9 Eye pain, % rTMS: 6.1 vs. sham: 1.9 GI disorders toothache, % rTMS: 7.3 vs. sham: 0.6 Application site discomfort, % rTMS: 10.9 vs. sham: 1.3 Application site pain, % rTMS: 35.8 vs. sham: 3.8 Facial pain, % rTMS: 6.7 vs. sham: 3.2 Muscle twitching, % rTMS: 20.6 vs. sham: 3.2 Pain of skin, % rTMS: 8.5 vs. sham: 0.6] *P* = NR

GI = gastrointestinal; MedRA = Medical Dictionary for Regulatory Activities; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*This study came from an unpublished source (conference proceeding).

Table 57. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Berman et al., 2000[88] RCT SECL Fair	**rTMS (n = 10)** High frequency, 10 sessions **Sham (n = 10)**	**SECL** Headache, %: rTMS: 60 vs. sham: 50 *P* = NR Difficulty starting urination (ordinal scores from 0, none at all, to 3, severe): rTMS: 2.0 vs. sham: 1.1 *P* = 0.03 No significant difference between groups after correction for multiple comparisons (data NR)

Table 57. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder (continued)

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Bretlau et al., 2008[89] RCT UKU side effect scale Fair	**rTMS (n = 25)** High frequency, 15 sessions over 3 weeks **Sham (n = 24)** Both groups received 20 mg escitalopram	**UKU side effect scale, mean scores** Concentration difficulties: At week 3 rTMS: 1.43 vs. sham: 1.52 At week 12 rTMS: 0.71 vs. sham: 1.22 *P* < 0.05 Tension/inner unrest, tremor, akathisia, nausea, diarrhea, sweating, diminished sexual desire, headache, memory impairment, dry mouth, palpitations, and micturia: No significant difference between groups

mg = milligram; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SECL = Side Effect Checklist; UKU = Udvaig for Kliniske Undersogsler; vs. = versus

The other Tier 2 RCT (N = 49) compared rTMS with sham along with escitalopram (20 mg) in both groups and used the Udvaig for Kliniske Undersogsler (UKU) side-effect scale to assess side effects.[89] Among the specific side effects assessed, they found no significant difference in headaches between groups. At 12-week followup, significantly more patients in the sham procedure group had difficulties concentrating than did rTMS patients (1.22 versus 0.71 on 0 to 3 scale, $P < 0.05$).

Tier 3

There were no eligible studies.

Vagus Nerve Stimulation Versus Sham

There were no eligible studies in an MDD-only population and one study in an MDD/bipolar population in Tier 1. There were no eligible studies in Tiers 2 or 3.

Tier 1

There were no eligible studies in an MDD-only population and one study in an MDD/bipolar population.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Table 58 shows a Tier 1 RCT (N = 235) that compared VNS versus sham.[98] The study used the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) dictionary to assess adverse events. Many adverse events were listed, but no statistical analysis was conducted in the article. Numerous adverse events were more commonly reported in the VNS group than the sham group (*P* = NR). These included voice alteration (68% vs. 38%), cough increased (29% vs. 9%), dyspnea (23% vs. 14%), dysphasia (21% vs. 11%), and neck pain (21% vs. 10%) (for all *P*

= NR). One participant underwent device explantation due to infection. Eleven patients (4 in VNS group and 7 in sham group) had worsening depression requiring hospitalization.

Table 58. Adverse events assessed systematically of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Rush et al., 2005[98] RCT COSTART dictionary. Fair	**VNS (n = 119)** 10 weeks of VNS therapy with continued medications **Sham (n = 116)**	**COSTART Dictionary** (VNS vs sham)* Voice alteration (68% vs. 38%) Cough increased (29% vs. 9%) Dyspepna (23% vs. 14%) Dysphasia (21% vs. 11%) Neck pain (21% vs. 10%) Paresthesia (16% vs. 10%) Vomiting (11% vs. 5%) Laryngismus (11% vs. 2%) Dyspepsia (10% vs. 5%) Wound Infection (8% vs. 2%) Palpitations (8% vs. 2%) *article reports only AEs VNS ≥ 1.5 frequency of sham For all specific adverse events, *P* = NR Overall serious adverse events, n: VNS: 16 vs. sham: 14 (12 events in 11 patients [VNS: 4, sham: 7] were cases of worsening depression requiring hospitalization)

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; VNS = vagus nerve stimulation

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Key Question 4c: Tolerability as Measured by Withdrawals due to Adverse Events—Overview

Withdrawals due to an adverse event illustrate the general tolerability of treatments for TRD. People who cannot tolerate the adverse effects of the treatments fall into this category. Overall, reporting of withdrawals due to adverse events was limited for some comparisons by the fact that no statistical significance was reported by the authors when withdrawals occurred.

Overall, 21 studies reported withdrawals due to adverse events (Table 59). When considering only studies conducted in TRD (Tier 1) MDD-only patients, we identified one head-to-head trial of ECT versus rTMS[123] and four rTMS versus sham studies (five articles).[69,71,76,77,99] In a Tier 1 MDD/bipolar population, we identified four studies that compared rTMS to sham[18,74,80,81] and one study that compared VNS to sham.[98]

Table 59. Number of good- and fair-quality studies by TRD tier and diagnostic mix that assess withdrawals due to adverse events for KQ 4c

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	1	0
ECT vs. rTMS	Tier 3: Probable	0	2 additional
ECT vs. sham	Tier 3: Probable	0	1 additional
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	4	4
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	3 additional	0
rTMS vs. sham	Tier 3: Probable	0	2 additional
VNS vs. sham	Tier 1: ≥ 2 treatment failures	0	1
CBT vs. usual care	Tier 2: ≥ 1 treatment failure	1 additional	2 additional

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Additional eligible studies were found in Tiers 2 and 3. Three studies (8 articles) were conducted in Tier 2 patients with MDD comparing rTMS to sham.[83,86,87,115,116,119,124,125] Two Tier 3 studies comparing rTMS versus sham in an MDD/bipolar mix population were identified.[90,91] One Tier 2 study in patients with MDD[94] and two Tier 2 studies in patients with an MDD/bipolar mix (three articles) compared CBT versus usual care.[93,95,96] Two head-to-head studies (four articles) in Tier 3 compared ECT with rTMS[61-63,126] and one study compared ECT to sham[68] in a population diagnosed with MDD and bipolar disorder.

Strength of Evidence: Tier 1 (TRD)

Few studies provide relevant data (Table 60). One small study showed no differences in withdrawals in ECT versus rTMS (statistical significance not reported), leading to a grade of low strength of evidence that withdrawals due to adverse events were greater with ECT than rTMS. In the rTMS versus sham group the results are mixed, with the data not providing a clear direction of effect of the treatment on withdrawals due to adverse events, resulting in a strength grade of insufficient. There was low strength of evidence that there were greater withdrawals due to adverse events in the vagus nerve stimulation group compared to sham.

Table 60. Strength of evidence: withdrawals due to adverse events -- Tier 1

Comparison	Number Of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. rTMS	1; 30	Medium 1 fair prospective cohort study	Unknown	Direct	Imprecise	No differences between groups in ECT vs. rTMS *P* = NR Low
rTMS vs. sham	7; 277	Medium 7 RCTs 1 good, 6 fair	Inconsistent	Inirect	Imprecise	Mixed results Insufficient
VNS vs. sham	1; 235	Low RCT Good	Unknown	Indirect	Precise	More withdrawals due to AEs in the VNS group *P* = NR Low

AE = adverse event; ECT = electroconvulsive therapy; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Key Points

Withdrawals due to adverse events illustrate the general tolerability of treatments for treatment-resistant depression. Overall, reporting of withdrawals due to adverse events was limited by the fact that no tests of statistical significance were performed by the authors when withdrawals occurred.

Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1 consists of one prospective cohort study in an MDD population and none in an MDD/bipolar population (Table 61). Tier 2 has no eligible studies. Tier 3 has no studies in MDD-only patients and two RCTs in MDD/bipolar mix patients.

Tier 1

There was one prospective cohort study in an MDD population and none in an MDD/bipolar population.

MDD-Only

One fair-quality prospective cohort study[123] adequately reported withdrawals due to adverse events. This observational study reported greater withdrawals in the ECT versus rTMS group (7.1% versus 0%, respectively).[123] Sample sizes were small, all with less than 20 patients per study arm (Table 61).

Table 61. Withdrawals due to adverse events of ECT versus rTMS: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Schulze-Rauschenbach et al., 2005[123] Prospective cohort 1 week (post-test measurement 8.8 days after txt) Fair	**ECT (n = 14)** Right unilateral txt for 2 weeks **rTMS (n = 16)** High frequency, mean 10.8 sessions (SD 1.4)	Due to AEs, n (%): ECT: 1 (7.1) rTMS: 0 (0) *P* = NR

AE = adverse event; ECT = electroconvulsive therapy; NR = not reported; P = p-value; SD = standard deviation; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and two RCTs in MDD/bipolar mix patients.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two RCTs (four articles, one good-quality and one fair-quality).[61-63,126] They reported no withdrawals due to adverse events (Table 62).

Table 62. Withdrawals due to adverse events of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
McLoughlin et al., 2007,[61] Eranti et al., 2007,[62] and Knapp et al., 2008[63] RCT 3 weeks Good	**ECT (n = 24)** 82% bilateral, mean sessions 6.3 (SD 2.5) **rTMS (n = 22)** High frequency, 15 sessions	Due to AEs: 0
O'Connor, 2003[126] Prospective cohort Up to 4 weeks Fair	**ECT (n = 14)** Unilateral, 3 times per week for 2 to 4 weeks **rTMS (n = 14)** High frequency, 10 sessions	Due to AEs: 0

AE = adverse event; ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Electroconvulsive Therapy Versus Sham

Tier 1 has no eligible studies (Table 63). Tier 2 has no eligible studies. Tier 3 has no studies in MDD-only patients and one RCT in MDD/bipolar mix patients.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and one RCT in MDD/bipolar mix patients (Table 63).

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One study in a population with "severe endogenous depression" referred for ECT.[68] Withdrawals due to adverse events were 5.7 percent in the ECT arm and 0 in the simulated ECT arm (see Table 63).

Table 63. Withdrawals due to adverse events of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Johnstone et al., 1980[68] RCT 3 weeks Fair	**ECT (n = 35)** Bilateral, 8 sessions **Sham (n = 35)**	Due to AEs (%): ECT: 5.7 Sham: 0 *P* = NR

AE = adverse event; ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1 contains four RCTs in patients with MDD-only (Table 64) and three RCTs in MDD/bipolar patients (Table 65). There are three RCTs in an MDD-only population and no

Table 64. Withdrawals due to adverse events of rTMS versus sham: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Avery et al., 2006[77] and Avery et al., 2007[99] RCT 4 weeks Good	**rTMS (n = 35)** High frequency, 15 sessions **Sham (n = 33)**	Due to AEs: 0
Boutros, et al., 2002[69] RCT 2 weeks Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 9)**	Due to AEs: 0
Garcia-Toro et al., 2006[71] RCT 2 weeks Fair	**rTMS-1 (n = 10)** High frequency plus low frequency, 10 sessions **rTMS-2 (n = 10)** Same as above with individually assessed location **Sham: (n = 10)**	Due to AEs: 0
Holtzheimer et al., 2004[76] RCT 2 weeks Fair	**rTMS (n = 7)** High frequency, 10 sessions **Sham (n = 8)**	Due to AEs: 0

AE = adverse event; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Table 65. Withdrawals due to adverse events of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Fitzgerald et al., 2006[18] RCT 6 weeks Fair	**High plus low rTMS (n = 25)** High-frequency rTMS up to 30 sessions plus low-frequency rTMS up to 30 sessions **Sham (n = 25)**	Due to AEs: 0
Fitzgerald et al., 2003[80] RCT Phase I: 2 weeks Fair	**High rTMS (n = 20)** High frequency, 10 sessions **Low rTMS (n = 20)** Low frequency, 10 sessions **Sham (n = 20)**	Due to AEs: 0
Pallanti et al., 2010{#2551} RCT 3 weeks Fair	**Low plus High rTMS (n = 20)** Low then high frequency, 15 sessions **rTMS (n = 20)** Low frequency, 15 sessions **Sham (n = 20)**	Due to AEs, n (%): Low plus high rTMS: 0 (0) Low rTMS: 0 (0) Sham: 0 (0) *P* = NR
Su et al., 2005[81] RCT 2 weeks Fair	**20 Hz rTMS (n = 11)** High frequency (20 Hz), 10 sessions **5 Hz rTMS (n = 11)** High frequency (5 Hz),10 sessions **Sham (n = 11)**	Due to AEs, %: All rTMS: 9.1 20 Hz rTMS: 0 5 Hz rTMS: 17 Sham: 0 *P* = NR

AE = adverse event; Hz = hertz; n = number; RCT = randomized controlled trial, rTMS = repetitive transcranial magnetic stimulation

eligible studies in MDD/bipolar diagnosis patients in Tier 2. In Tier 3 there were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis.

Tier 1

There are three RCTs in patients with MDD-only and four RCTs in MDD/bipolar patients.

MDD-Only

Table 64 presents one good and three fair RCTs that reported no withdrawals in either patients treated with rTMS or sham.[69,71,76,77,99]

MDD/Bipolar mix

Four fair RCTs reported withdrawals due to adverse events in patients previously treated two or more times for depression, as seen in Table 65. Three of the studies showed no withdrawals due to adverse events.[18,74,80] There was one study that showed a difference in withdrawals due to adverse events (rTMS 9.1% versus none for sham).[81] There are important differences between this study and the others in this group, primarily in the strength of the intervention. As can be seen, the RCT that showed differences in withdrawals due to adverse events used more pulses per session, 1,600 versus 750 to 1,000 and 20 Hz versus 10 Hz, which could explain the differences in withdrawals due to adverse events within this group.

Tier 2

There are three RCTs in an MDD-only population and no eligible studies in MDD/bipolar diagnosis patients (Table 66).

Table 66. Withdrawals due to adverse events of rTMS versus sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
George et al., 2010[83] RCT 3 weeks of txt Good	**rTMS (n = 92)** High frequency, 15 sessions **Sham (n = 98)**	Due to AEs, %: rTMS: 5.4 Sham: 0 *P* = NR
O'Reardon, 2007,[87] Janicak, 2007[115] and Solvason, 2007[116] Janciak et al., 2008[125] and Janicak et al., 2010[119] RCT 4 weeks primary endpoint Fair	**rTMS (n = 165)** High frequency, 20-30 sessions **Sham (n = 160)**	Due to AEs, %: rTMS: 4.2 Sham: 3.4 *P* = NR
Stern et al., 2007[86] RCT 2 weeks of txt Fair	**High rTMS (n = 10)** High frequency, 10 sessions **Low-left rTMS (n = 10)** Low frequency (Left-DLPFC), 10 sessions **Low rTMS (n = 10)** Low frequency, 10 sessions **Sham (n = 15)**	Due to AEs, %: High rTMS: 0 Low-left rTMS: 50 Low rTMS: 0 Sham: 20 *P* = NR

AE = adverse event; DLPFC = dorsolateral prefrontal cortex; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD-Only

One relatively large (n = 325) study compared Tier 2 patients in an MDD-only population.[87,115,116,119,124,125] The withdrawals due to adverse events were similar in the rTMS group (4.2%) versus sham (3.4%) over the 4-week time period. Another decent size study (N = 190) compared withdrawals due to adverse events between rTMS at 5.4 percent to sham at 0 percent.[83] Additionally a small study (n = 45) compared withdrawals due to adverse events in four arms, high rTMS (n = 10), low-left rTMS (n = 10), low rTMS (n = 10) and sham (n = 15).[86] Two arms had no withdrawals but the low-left rTMS had 50 percent withdrawals due to adverse event rate and 30 percent in the sham group.

MDD/Bipolar mix

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis (Table 67).

Table 67. Withdrawals due to adverse events of rTMS versus sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Bortolomasi et al., 2006[90] RCT 1 week Fair	**rTMS (n = 12)** High frequency, 5 sessions **Sham (n = 7)**	Due to AEs: 0
George et al., 1997[91] RCT, crossover Primary endpoint after 2 weeks of txt Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 12)**	Due to AEs: 0

AE = adverse event; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

There were two small studies (n = 19 and 24) in a Tier 3 MDD/bipolar mix population comparing rTMS to sham.[90,91] Neither had any withdrawals due to adverse events.

Vagus Nerve Stimulation Versus Sham

There were no eligible studies in patients with MDD-only and one RCT in patients with an MDD/bipolar diagnosis in Tier 1. In Tiers 2 and 3, there were no eligible studies.

Tier 1

There were no eligible studies in patients with MDD-only and one RCT in patients with an MDD/bipolar mix diagnosis (Table 68).

Table 68. Withdrawals due to adverse events of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Rush et al., 2005[98], RCT 10 weeks Good	**VNS (n = 112)** 10 weeks of VNS therapy with continued medications **Sham (n = 110)**	Due to AEs, %: VNS: 2.7 Sham: 0 *P* = NR

AE = adverse event; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; VNS = vagus nerve stimulation

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One good-quality RCT (N = 222) comparing VNS to sham-control in a Tier 1 population reported 2.7 percent withdrawals due to adverse events in the VNS group compared with none in the sham-control group over a 10-week treatment period.[98]

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Cognitive Behavioral Therapy Versus Usual Care

There were no eligible studies in Tier 1. In an MDD population there was one eligible study and 2 studies in an MDD/bipolar mix population in Tier 2. There were no eligible studies in Tier 3.

Tier 1

There were no eligible studies.

Tier 2

There was one study in MDD-only and 2 studies in patients with an MDD/bipolar mix.

MDD-Only

One RCT reported withdrawals due to adverse events in 491 patients randomized to either medication alone or medication plus psychotherapy over 12 weeks of treatment (Table 69).[94] The medication-alone arm had 2.1 percent versus 0.8 percent withdrawals in the medication plus psychotherapy due to adverse events.

Table 69. Withdrawals due to adverse events of CBT versus sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Kocsis et al., 2009[94] RCT 12 weeks Fair	**CBT plus medication (n =395)** Cognitive behavioral analysis system of psychotherapy (n = 200) 16-20 sessions; brief supportive psychotherapy (n = 195) 16-20 sessions **Medication only (n=96)**	Due to AEs: CBT plus medication: 3 (0.8%) Medication only: 2 (2.1%) *P* = NR

AE = adverse event; CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

MDD/Bipolar mix

Two RCTs (four articles, one good-quality, one fair-quality) comparing CBT to some form of usual care reported no withdrawals due to adverse events, as shown in Table 70.[93,95,96,120] These studies ranged in duration from 16 weeks of treatment to 12-month followup periods.

Tier 3

There were no eligible studies.

Table 70. Withdrawals due to adverse events of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Harley, 2008[93] RCT 16 weeks Fair	**CBT ([DBT] (n = 13)** 16-sessions of dialectical behavior therapy skill training **Control (n = 11)** Waitlist	Due to AEs: 0
Paykel, 1999,[95] Scott, 2000,[96] and Scott, 2003[120] RCT 20 weeks Good	**Cognitive Therapy (n = 80)** 16 sessions of cognitive therapy plus clinical management **Clinical Management (n = 78)** Clinical management – patients visited psychiatrist every 4 weeks and continued on current medication	Due to AEs: 0

AE = adverse event; CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

Key Question 4d: Adherence as Measured by Overall Withdrawals—Overview

Of 64 included studies, two studies reporting compliance indicated a 100 percent rate[66,71] and 1 reported a 63 percent adherence rate.[83] Overall withdrawals were used as a proxy to capture compliance as it was recorded more frequently. Out of the 64 included studies, 26 studies (32 articles) reported total withdrawals (for any reason) during treatment (Table 71).

Table 71. Number of good- and fair-quality studies by TRD tier and diagnostic mix that assess overall withdrawals for KQ 4d

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	2	0
ECT vs. rTMS	Tier 3: Probable	0	3 additional
ECT vs. sham	Tier 3: Probable	1 additional	1 additional
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	4	3
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	3 additional	2 additional
rTMS vs. sham	Tier 3: Probable	0	2 additional
CBT vs. usual care	Tier 2: ≥ 1 treatment failure	2 additional	2 additional

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

When considering only studies conducted in Tier 1 patients with MDD, there were two head-to-head trials of ECT versus rTMS[58,123] and three rTMS versus sham studies (four articles).[71,76,77,99] There were five Tier 1 studies, conducted in an MDD/bipolar population that compared rTMS to sham.[18,69,80-82]

Additional eligible studies were found in Tiers 2 and 3. In Tier 2 MDD-only populations, we identified three studies (eight articles) comparing rTMS to sham[83,86,87,115,116,119,124,125] and two studies in an MDD/bipolar mix population.[88,89] We also identified two studies in MDD-only populations comparing CBT to usual care.[94,102] In Tier 2 MDD/bipolar mix populations, we identified two studies (three articles) comparing CBT versus usual care.[93,95,96] Three head-to-

head studies (four articles) in Tier 3 compared ECT with rTMS in a population diagnosed with MDD and bipolar disorder.[60-63,126] There are two Tier 3 studies that compared ECT to sham, one in an MDD-only group[67] and one in an MDD and bipolar population.[68] There are also two Tier 3 studies that compared rTMS to sham in a MMD and bipolar population.[90,91]

Strength of Evidence: Tier 1 (TRD)

The data addressing overall withdrawals (Table 72) for ECT versus rTMS showed greater withdrawals in ECT when compared with rTMS (*P* = NR). For rTMS versus sham, mixed results were found. Strength of evidence is low for ECT versus rTMS and insufficient for rTMS versus sham.

Table 72. Strength of evidence: overall withdrawals during treatment -- Tier 1

Comparison	Number Of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. rTMS	2; 72	Medium 1 fair RCT 1 fair prospective cohort study	Consistent	Direct	Imprecise	ECT group had higher number of withdrawals *P* = NR Low
rTMS vs. sham	8; 325	Medium 8 RCTs 1 good 7 fair	Inconsistent	Indirect	Imprecise	Mixed results Insufficient

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 4d: Adherence as Measured by Overall Withdrawals—Key Points

Of the 27 studies with relevant data, there were only three studies (three articles) that assessed adherence or compliance during treatment.[66,71,83] Two reported that all patients completed all required treatments as specified in the protocol and one reported an overall adherence rate of 62 to 64 percent. As a proxy to explore adherence, we chose overall withdrawals, which are found in 10 Tier 1 studies and an additional 15 studies in Tiers 2 and 3.

Overall, reporting of withdrawals during treatment was limited by the fact that statistical significance was not reported. Studies were generally small and unlikely to have had power to show statistical or clinical significance, methods varied, and there was significant heterogeneity across the populations studied.

Key Question 4d: Adherence as Measured by Overall Withdrawals—Detailed Analysis

As shown in Table 73, there were only three studies that reported adherence or compliance.[66,71,83] Two of them reported 100 percent compliance and one reported adherence of 62 to 64 percent.

Table 73. Adherence/compliance for all comparable interventions: all tiers

Author, Year Design Duration Tier Quality	Intervention and Sample Size Study Details	Results
Folkerts et al.[66] RCT: patient status NR 4 weeks Tier 1 Fair	**ECT (n = 21)** Right unilateral, mean txts = 7.2 sessions (2-3 weeks) **Pharmacotherapy (n = 18)** Paroxetine 40 mg (max 50 mg/d, mean daily dosage 44 mg/day	All patients continued their respective therapies through scheduled end of treatment phase
Garcia-Toro et al., 2006[71] RCT: outpatient 2 weeks Tier 1 Fair	**rTMS-1 (n = 10)** High frequency plus low frequency, 10 sessions **rTMS-2 (n = 10)** Same as above but with individually assessed location **Sham: (n = 10)**	All completed 10 rTMS sessions
George et al., 2010[83] RCT Tier 2 Good	**rTMS (n = 92)** High frequency, 15 sessions **Sham (n = 98)**	Fully adherent to treatment, % rTMS: 62 Sham: 64

ECT = electroconvulsive therapy; mg/day = milligram per day; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

There were two studies, an RCT and a prospective cohort study, in Tier 1. There were no eligible studies in Tier 2; in Tier 3 there were no MDD studies, and in an MDD/bipolar mix there were two RCTs and one prospective cohort study.

Tier 1

There were two studies, an RCT and a prospective cohort study.

MDD-Only

There are two Tier 1 studies that compared ECT to rTMS and reported overall withdrawals, as seen in Table 74. The first is a small RCT (n = 42) that resulted in more withdrawals in the ECT group of 15.1 percent than the rTMS group at 9.1 percent (P = NR).[58] The second study was a small prospective cohort study (N = 30).[123] Similar to the RCT, it showed that the ECT group experienced higher overall withdrawals of 7.1 percent versus 0 percent in the rTMS group, but significance is not reported.

Table 74. Overall withdrawals of ECT versus rTMS: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Rosa et al., 2006[58] RCT Up to 4 weeks Fair	**ECT (n = 20)** % bilateral NR, mean sessions: 10 (SD 1.5) **rTMS (n = 22)** High frequency, 10-20 sessions (2-4 weeks)	Overall, %: ECT: 15.0 rTMS: 9.1 *P* = NR
Schulze-Rauschenbach et al., 2005[123] Prospective cohort 1 week (post-test measurement 8.8 days after txt) Fair	**ECT (n = 14)** Right unilateral treatment for 2 weeks, mean # sessions 9.9 (SD 2.7) **rTMS (n = 16)** High frequency, mean sessions: 10.8 (SD 1.4)	Overall, %: ECT: 7.1 rTMS: 0 *P* = NR

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt = treatment

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no MDD studies and in an MDD/bipolar mix there were two RCTs and one prospective cohort study.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

As shown in Table 75, three studies report overall withdrawals in a Tier 3 population comparing ECT to rTMS. A good-rated RCT reported overall withdrawals in the ECT group of 0 percent compared to 25 percent in the rTMS arm (*P* = NR).[61-63] Another RCT reported overall withdrawals in the ECT group of 26.7 percent compared to 33.3 percent in the rTMS arm.[60]A small prospective cohort reported no overall withdrawals in either arm.[126]

Electroconvulsive Therapy Versus Sham

Tier 1 has no eligible studies (Table 76). Tier 2 has no eligible studies. Tier 3 has one study in MDD-only patients and one RCT in MDD/bipolar mix patients.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

Two trials comparing ECT with sham stimulation were identified in Tier 3.

MDD-Only

There was one study, in Table 76, in a population with "primary depressive illness" referred for ECT.[67] Overall withdrawals were recorded as 15.4 percent in the ECT group versus 8.3 percent in the simulated ECT group (*P* = NR).

Table 75. Overall withdrawals of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Withdrawals during treatment
McLoughlin et al., 2007,[61] Eranti et al., 2007,[62] and Knapp et al., 2008[63] RCT 3 weeks Good	**ECT (n = 24)** 82% bilateral, mean sessions: 6.3 (SD 2.5) **rTMS (n = 22)** High frequency, 15 sessions	Overall, % ECT: 0 rTMS: 25 *P* = NR
Hansen, 2010[60] RCT 3 weeks Fair	**ECT (n = 30)** 100% unilateral, 9 sessions **rTMS (n = 30)** Low frequency, 15 sessions	Overall, % ECT: 26.7 rTMS: 33.3 *P* = NR
O'Connor, 2003[126] Prospective cohort Up to 4 weeks Fair	**ECT (n = 14)** Unilateral, 3 times per week for 2 to 4 weeks **rTMS (n = 14)** High frequency, 10 sessions	Overall: 0

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Table 76. Withdrawals due to adverse events of ECT versus sham: Tier 3, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
West, 1981[67] RCT Up to 3 weeks Fair	**ECT (n = 13)** Bilateral, 6 sessions **Sham (n = 12)**	Overall withdrawals (%): ECT: 15.4 Sham: 8.3 *P* = NR

ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar mix

There was one study, shown in Table 77, in a population with "severe endogenous depression" referred for ECT.[68] Overall withdrawals were recorded as 11.4 percent in the ECT group and 11.4 percent in the simulated ECT group (*P* = NR).

Table 77. Withdrawals due to adverse events of ECT versus sham: Tier 3, MDD and and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Johnstone et al., 1980[68] RCT 3 weeks Fair	**ECT (n = 35)** Bilateral, 8 sessions **Sham (n = 35)**	Overall withdrawals (%): ECT: 11.4 Simulated ECT: 11.4 *P* = NR

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation.

Repetitive Magnetic Stimulation Versus Sham

Tier 1 contains four RCTs in patients with MDD-only and three RCTs in MDD/bipolar patients. There are three RCTs in an MDD-only population and two eligible studies in an MDD/bipolar population in Tier 2. In Tier 3 there were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix population.

Tier 1

MDD-Only

There are four RCTs that compare overall withdrawals in rTMS versus sham in a Tier 1 population (see Table 78). Two report that there are no withdrawals in either the rTMS or sham arms.[71,76] An RCT conducted in 68 patients showed an overall withdrawal rate of 9.1 percent in the rTMS arm and 8.6 percent in the sham arm (*P* = NR).[77,99] Another RCT of 21 patients had overall withdrawals of 8.3 percent in the rTMS group and 30.0 in the sham group.[69]

Table 78. Overall withdrawals of rTMS to sham: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Avery et al., 2006[77,99] RCT 4 weeks Good	**rTMS (n = 35)** High frequency, 15 sessions **Sham (n = 33)**	Overall, %: rTMS: 9.1 Sham: 8.6 *P* = NR
Boutros, et al., 2002[69] RCT 2 weeks Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 9)**	Overall, %: rTMS: 8.3 Sham: 30.0 *P* = NR
Garcia-Toro et al., 2006[71] RCT 2 weeks Fair	**rTMS-1 (n = 10)** High frequency plus low frequency, 10 sessions **rTMS-2 (n = 10)** Same as above but with individually assessed location **Sham: (n = 10)** Double winged coil angled at 45 degrees	Overall: 0
Holtzheimer et al., 2004[76] RCT 2 weeks Fair	**rTMS (n = 7)** High frequency, 10 sessions **Sham (n = 8)**	Overall: 0

n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

MDD/Bipolar mix

Four RCTs comprise the MDD/bipolar mix in a Tier 1 population, as shown in Table 79. One RCT conducted in 40 patients had zero withdrawals in any arm.[80] Another RCT with 48 patients also had zero withdrawals.[82] Another small study (N = 33) had 9.1 percent overall withdrawals in the rTMS and sham groups.[81] A larger study, 50 patients, had 0 percent overall withdrawals in the rTMS group and 12 percent in the sham group.[18]

Table 79. Overall withdrawals of rTMS to sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Fitzgerald et al., 2006[18] RCT 6 weeks Fair	**High plue Low rTMS (n = 25)** High frequency plus low frequency, up to 30 sessions **Sham (n = 25)**	Overall, %: rTMS: 0 Sham: 12 *P* = NR
Fitzgerald et al., 2003[80] RCT Phase I: 2 weeks Phase II: NA Fair	**High rTMS (n = 20)** High frequency, 10 sessions **Low rTMS (n = 20)** Low frequency, 10 sessions **Sham (n = 20)**	Overall: 0
Su et al., 2005[81] RCT 2 weeks Fair	**20 Hz rTMS (n = 11)** High frequency (20 Hz), 10 sessions **5 Hz rTMS (n = 11)** High frequency (5 Hz),10 sessions s **Sham (n = 11)**	Overall, % 10 Hz rTMS and 5 Hz rTMS: 9.1 Sham: 9.1 *P* = NR
Triggs et al., 2010[82] RCT 2 weeks Fair	**High rTMS (n = 18)** High frequency, 10 sessions **High right rTMS (n = 16)** High frequency to the right prefrontal cortex, 10 sessions **Sham left (n = 7)** **Sham right (n = 7)** NOTE: Patients in all groups also received a social support intervention	Overall: 0

Hz = Hertz; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tier 2

MDD-Only

There were three RCTs in Tier 2 in MDD-only patients, as seen in Table 80. A relatively large study, 325 patients, had overall withdrawals of 13.3 percent in the rTMS arm and 16.3 percent in the sham arm.[87,115,116,119,124,125] The second study, conducted with 190 patients, had overall withdrawals of 12 percent in the rTMS arm and 9 percent in the sham arm.[83] A small study (n = 45) compared overall withdrawals in four arms, high rTMS (n = 10), low-left rTMS (n = 10), low-right rTMS (n = 10), and sham (n = 15). Two arms had no withdrawals but the low-left rTMS had a 20 percent overall withdrawal rate and 6.7 percent in the sham group.[86]

Table 80. Overall withdrawals of rTMS to sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
George et al., 2010[83] RCT Up to 6 weeks of txt Good	**rTMS (n = 92)** High frequency, 15 sessions **Sham (n = 98)**	Overall, % rTMS: 12 Sham: 9 *P* = NR
O'Reardon, 2007[87,115,116,119,124,125] RCT 4 weeks primary endpoint Fair	**rTMS (n = 165)** High frequency, 20-30 sessions **Sham (n = 160)**	Overall, % rTMS: 13.3 Sham: 16.3 *P* = NR
Stern et al., 2007[86] RCT 2 weeks of txt Fair	**High rTMS (n = 10)** High frequency, 10 sessions **Low-left rTMS (n = 10)** Low frequency, (1 Hz), Left DLPFC, 10 sessions **Low rTMS (n = 10)** Low frequency, 10 sessions **Sham (n = 15)**	Overall: High rTMS: 0 Low-left rTMS: 20 Low rTMS: 0 Sham: 6.7 *P* = NR

DLPFC = dorsolateral prefrontal cortex; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD/Bipolar mix

Table 81 provides the two studies that were found in a Tier 2 MDD/bipolar population.[88,89] Overall withdrawals were 0 percent in the rTMS arm and 30 percent in the sham arm. However, no significance was reported.[88] The final study in this group had overall withdrawals of 12.0 percent in the rTMS arm versus 4.2 percent but significance is not reported.[89]

Table 81. Overall withdrawals of rTMS to sham: Tier 2, MDD and and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Berman et al, 2000[88] RCT 2 weeks Fair	**rTMS (n = 10)** High frequency, 10 sessions **Sham (n = 10)**	Overall: rTMS: 0 Sham: 30 *P* = NR
Bretlau et al., 2008[89] RCT 3 weeks Fair	**rTMS (n = 25)** High frequency, 15 sessions over 3 weeks **Sham (n = 24)** Both groups received 20 mg escitalopram	Overall, %: rTMS: 12.0 Sham: 4.2 *P* = NR

mg = milligram; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tier 3

There were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two small studies, 19 and 24 patients, compared rTMS and sham in Tier 3 subjects, as seen in Table 82.[90,91] Neither of these studies had any overall withdrawals.

Table 82. Overall withdrawals of rTMS to sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Bortolomasi et al., 2006[90] RCT 1 week Fair	**rTMS (n = 12)** High frequency, 5 sessions **Sham (n = 7)**	Overall: 0
George et al., 1997[91] RCT, crossover Primary endpoint after 2 weeks of txt Fair	**rTMS (n = 12)** High frequency, 10 sessions **Sham (n = 12)**	Overall: 0

N = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Cognitive Behavioral Therapy Versus Usual Care

There were no eligible studies in Tier 1. Tier 2 had two studies in patients with MDD-only and two studies in patients diagnosed with MDD/bipolar mix; there were no eligible studies in Tier 3.

Tier 1

There were no eligible studies.

Tier 2

There were two studies in patients with MDD-only and two studies in patients diagnosed with MDD/bipolar mix.

MDD-Only

Table 83 provides two studies, one small study of 32 patients[102] and one larger study of 491 patients,[94] conducted in MDD-only Tier 2 patients. In the smaller study, the overall withdrawal rate was 16.7 percent in the CBT arm and 42.9 percent in the usual care arm. Statistical significance was not reported; the CBT arm had 26 subjects compared to 6 in the usual care arm. The larger study had overall withdrawals of 16.6 percent in the medication arm and 13.2 percent in the medication plus psychotherapy arm (P = NR).

MDD/Bipolar mix

Two studies (four articles) compared CBT to usual care with mixed results in patients with MDD/bipolar mix in Tier 2 (see Table 84). The smaller one, 24 patients, had an overall withdrawal rate of 23.1 percent in the CBT arm and 18.2 percent in the waitlist control arm.[93] A larger study, 158 patients, had overall withdrawals of 15.4 percent in the CBT arm versus 23.8 percent in the usual care arm.[95,96,120] For either study, statistical significance was not reported.

Table 83. Overall withdrawals of CBT versus medication: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Kocsis et al., 2009[94] RCT 12 weeks Fair	**CBT plus medication (n =395)** Cognitive behavioral analysis system of psychotherapy (n = 200); 16-20 sessions; brief supportive psychotherapy (n = 195) 16-20 sessions **Medication only (n=96)**	Overall, % CBT plus medication: 13.2 Medication: 16.6 *P* = NR
Moore et al., 1997[102] RCT Active phase occurred during 12-month followup phase Fair	**CBT (n = 26)** Minimum of 4 treatments in 1st month, 2 treatments in 2nd month, and 1 per month following **Medication (n = 6)** Continued or new medication dose within recognized therapeutic threshold	Overall, % CBT: 16.7 Medication: 42.9 *P* = NR

CBT = cognitive behavioral therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial

Table 84. Overall withdrawals of CBT versus usual care: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Quality	Intervention and Sample Size Study Details	Results
Harley, 2008[93] RCT 16 weeks Fair	**CBT [DBT] (n = 13)** 16-session, once-weekly group covered the 4 dialectical behavior therapy skill sets **Control (n = 11)** Waitlist	Overall, % CBT: 23.1 Usual care: 18.2 *P* = NR
Paykel, 1999[95] and Scott, 2000[96] and Scott, 2003[120] RCT 20 weeks Good	**CBT (n = 80)** 16 cognitive behavioral therapy sessions plus clinical management **Clinical Management (n = 78)** Clinical management alone – patients visited psychiatrist every 4 weeks and continued on current medication	Overall, % CBT plus clinical management: 15.4 Clinical management: 23.8 *P* = NR

CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

Tier 3

There were no eligible studies.

Key Question 5: Efficacy and Harms for Selected Populations

Overview

Studies that focused on subgroups or included a subanalysis for a special population were eligible for consideration for this KQ. Most studies were excluded because the subgroup analysis was not comparative between groups, but rather descriptive within an intervention group. Two randomized controlled trials were in specific age populations, one Tier 1 study involving rTMS compared with sham[75] and one Tier 3 trial of ECT versus sham.[68,127,128] Three RCTs, one Tier 1 and two Tier 2, focused on post-stroke depression, comparing rTMS to a sham intervention[129,130] (Table 85).

Table 85. Number of good- and fair-quality studies by TRD tier and diagnostic mix of subpopulations presented in KQ 5

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. sham	Tier 3: Probable	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	2	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2	0

ECT, electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation.

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessment was made for three outcomes: change in depressive severity, response rate, and remission rate for the two Tier 1 trials comparing rTMS versus sham (Table 86). Remission rate was not addressed in the one younger adult age group trial. Strength of evidence is low for each outcome, given that there is only one small study for each subpopulation of interest. No *P* value was reported for the change in depressive severity; in the one age subpopulation trial, however, there was a significant difference favoring rTMS in response rates.

Table 86. Strength of Evidence: Efficacy and other comparative clinical outcomes of rTMS versus sham -- Tier 1, MDD

Comparison	Number of Studies; Subjects	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	2; 54	Low RCT Fair	Consistent	Indirect	Precise	rTMS > sham in young adult population (ages 18–37) rTMS > sham in older adults with post-stroke depression Low for age and for post-stroke depression
Response	2; 54	Low RCT Fair	Inconsistent	Indirect	Precise	rTMS > sham in young adult population (ages 18–37) No difference between rTMS and sham for older adults with post-stroke depression Low for age and for post-stroke depression
Remission	1;20	Low RCT Fair	NA	Indirect	Precise	No difference between rTMS and sham in older adults with post-stroke depression Low for post-stroke depression

RCT = randomized controlled trials; rTMS = repetitive transcranial magnetic stimulation

Key Points

We did not identify any head-to-head comparisons for this KQ.

Age

Two studies provide some evidence on the efficacy of nonpharmacologic treatments in two different age groups. One, a Tier 1 study, looked at rTMS in a young adult population (ages 18 to 37); the other was a Tier 3 study in middle-aged subjects (ages 30 to 69) using ECT. A greater decrease in depressive severity and a higher response rate was seen in the trial of severely depressed younger adults undergoing 20 sessions of rTMS compared with sham. However,

efficacy evidence is weaker for the 2-week trial of middle-aged adults with "severe endogenous depression," where the depressive severity data was only shown in a figure and noted that the completers analysis found a significantly greater decrease in depressive severity with the ECT compared with sham.

Post-stroke Depression

We found one Tier 1 and two Tier 2 trials in older patients with vascular depression. These trials showed a greater decrease in depressive severity in those receiving rTMS treatment versus sham. Two of the three trials found statistically significant improvements, but the third trial was underpowered to detect a difference. Response and remission rates were significantly greater in the active group only for the one trial that provided 15 sessions of rTMS over 3 weeks, in comparison to 10 sessions over 2 weeks in the other trials.

Detailed Analysis

We identified two relevant studies, both involving a comparison to a sham control (Table 87).

Table 87. Efficacy of ECT or rTMS versus sham for age subpopulations: all Tiers, MDD

Author, Year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
Johnstone et al., 1980[68,127,128] 4 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	**ECT (n = 35)** Bilateral, 8 sessions **Sham (n = 35)** **Treatment strategy** Switch - unclear if patients taking an AD at baseline. No AD allowed during the trial mITT	**Previous manic episodes:** Overall: 10% **Mean number of failed antidepressant trials:** ECT: NR Sham: NR **Baseline Depression** HAM-D_{17}, mean (SD) Reported in graph only	**HAM-D_{17}** Change, mean (SD) ECT: n= 31 Sham: n = 31 ECT vs. sham *P* < 0.01 (reported in graph only) **HAM-D_{17}** Response NR Remission NR	NR
Zheng et al., 2010 [75] 4 weeks Did not require failure in the current episode Tier 1 Fair	**rTMS (n = 19)** High frequency, 20 sessions **Sham (n = 15)** **Treatment strategy** Augment – all patients taking escitalopram 2+ weeks before trial	**Baseline Depression** HAM-D_{17}, mean (SD) rTMS: 24.6 (2.9) Sham: 24.6 (2.8) **Mean number of failed antidepressant trials:** NR	**HAM-D_{17}** Change, mean (SD) rTMS: -11.1 Sham: -1.7 *P* = NR **HAM-D_{17}** Response, n (%) rTMS: 12 (63.2) Sham: 1 (6.7) *P* = 0.001 Remission NR	NR

AD = antidepressants; ECT = electroconvulsive therapy; HAM-D_{17} = 17 item Hamilton Depression Scale; mITT = modified intent-to-treat analysis; NR = not reported; P = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Age

One Tier 1 trial was conducted in a younger population, ages 18 to 37. An augmentation study, it was a 4-week trial comparing high-frequency rTMS (n = 19) to sham rTMS treatment (n = 15).[75] At baseline, participants were severely depressed (HAM-D_{17} mean [SD] rTMS 24.6 [2.9] sham 24.6 [2.8]) and had been taking escitalopram for at least 2 weeks. In an ITT analysis,

participants in the rTMS group had a greater decrease in depressive severity (rTMS -11.1 sham -1.7, P = NR) and a higher response rate (rTMS 63.2% sham 6.7%, $P = 0.001$).

A Tier 3 trial of a middle-aged population (ages 30 to 69) with "severe endogenous depression" referred for ECT compared ECT (n = 35) with sham stimulation (n = 35) for a period of 4 weeks.[68] Participants in the study appear to have severe depression but these data are only reported in a graph. It is unclear what proportion of patients were on an antidepressant at study entry or had antidepressant failures in the past. During the trial, patients were not prescribed an antidepressant medication. Based on a completers analysis, the ECT group had a greater decrease in depressive severity compared to the sham group ($P < 0.01$).

Post-stroke Depression

One Tier 1 and two Tier 2 RCTs focus on patients over the age of 50 with MDD and determined to have vascular depression secondary to a vascular accident.[129,130] As shown in Table 88 below, all three compare high-frequency rTMS to a sham intervention and are of fair quality. All three studies were in moderately to severely depressed study populations (mean HAM-D_{17} scores between 17 and 20 in each group) and all discontinued any antidepressants they were receiving. No significant differences were reported for headache, local pain, or anxiety. No seizures occurred in either group.

Two experiments are presented in one article where all patients had at least one antidepressant medication failure.[129] The active intervention in the first study applied 10 sessions of rTMS to 15 patients (15 in the sham group). In a modified ITT analysis after 3 weeks of treatment, the rTMS group had a greater percentage decrease in HAM-D_{17} (33.1% versus 13.6%, $P = 0.04$) and tended to have a greater response rate, but the difference was not significant. Remission rates in each group were low, but also not significant. The second study increased the number of sessions to 15 and showed a greater decrease in depressive severity in the rTMS group with significantly improved response and remission rates after 3 weeks of treatment. In this experiment, 33 patients received 15 sessions (29 patients in sham group) and resulted in a greater percentage decrease in HAM-D_{17} (42.4% versus 17.5%, $P = 0.001$), response rate (39.4% versus 6.9%, $P = 0.003$) and remission (27.3% versus 3.4%, $P = 0.01$) in comparison to the sham intervention group.

In the third trial of 20 patients who had two antidepressant trial failures, 10 patients were treated with rTMS over 10 sessions and 10 received the sham treatment.[130] Those in the rTMS group showed a greater decrease in depressive severity, though the study did not have the power to adequately compare response and remission rates.[130] Mean baseline depressive severity was moderate, with both groups averaging between 20 and 21 points on the HAM-D_{17}. Antidepressants were tapered to discontinuation prior to enrollment, so patients were switched to rTMS or control. An ITT analysis at 3 weeks found that outcomes favored the rTMS group. Compared to control, rTMS produced a greater decrease in depressive severity (-7.3 versus -2.7, $P < 0.006$) and a greater likelihood of both response (3 out of 10 versus 0 out of 10) and remission (1 of 10 versus 0 of 10).

Table 88. Efficacy and other comparative harms outcomes of rTMS versus sham in post-stroke depression subpopulations: all Tiers, MDD

Author, year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
Jorge et al., 2008[129] Experiment 1 RCT, primary endpoint at 3 weeks, mITT Failure required in current episode Tier 2 Fair	**rTMS (n = 15)** High frequency, 10 sessions **Sham (n = 15)** **Concurrent medications** All antidepressants discontinued **Strategy** Switch **Definitions** Remission: HAM-D_{17} < 8 and did not meet criteria for major or minor depression	**Subgroup** Patients with stroke/cerebral vascular disease **Diagnosis,%** MDD: 100 **Baseline Depression:** HAM-D_{17} rTMS: 19.5 (5.8) Sham: 19.9 (5.4)	**HAM-D_{17}** Response, n (%) rTMS: 5 (33.3) Sham: 1 (6.7) *P* = 0.08 Remission, n (%) rTMS: 2 (13.3) Sham: 1 (6.7) *P* = 0.5 Change,% rTMS: -33.1 Sham: -13.6 *P* = 0.04	**Adverse Events** Headache,% rTMS: 5 (33) Sham: 4 (27) *P* = NR No differences in frequency of headaches; all headaches were mild and responded to low dose analgesics Local Pain, n (%) rTMS: 1 (7) Sham: 1 (7) *P* = NR Local discomfort, n (%) rTMS: 4 (27) Sham: 5 (33) No difference in frequency of local discomfort *P* = NR Anxiety, n (%) rTMS: 2 (13) Sham: 0 (0) *P* = NR Seizures, n rTMS: 0 Sham: 0 *P* = NR
Jorge et al., 2008[129] Experiment 2 RCT, primary endpoint at 3 weeks, mITT Failure required in current episode Tier 2 Fair	**rTMS (n = 33)** High frequency, 15 sessions **Sham** (n = 29) **Concurrent medications** All antidepressants discontinued **Strategy** Switch **Definitions** Remission: HAM-D_{17} <8 and did not meet criteria for major or minor depression	**Subgroup** Patients with stroke/cerebral vascular disease **Diagnosis,%** MDD: 100 **Baseline Depression, n** (%): HAM-D_{17} rTMS: 18.4 (3.4) Sham: 17.6 (5.6)	**HAM-D_{17}** Response, n (%) rTMS: 13 (39.4) Sham: 2 (6.9) *P* = 0.003 Remission rTMS: 9 (27.3) Sham: 1 (3.4) *P* = 0.01 Change,% rTMS: -42.4 Sham: -17.5 *P* < 0.001	**Adverse Events** Headache,% rTMS: 7 (21) Sham: 3 (10) No differences between groups in frequency of headaches; all headaches were mild and responded to low dose analgesics *P* = NR Local Pain, n (%) rTMS: 1 (3) Sham: 0 (0) *P* = NR Local discomfort, n (%) rTMS: 3 (9) Sham: 1 (3) No difference in frequency of local discomfort *P* = NR Anxiety, n (%) rTMS: 0 (0) Sham: 0 (0) *P* = NR Seizures, n rTMS: 0 Sham: 0 *P* = NR

Table 88. Efficacy and other comparative harms outcomes of rTMS versus sham in post-stroke depression subpopulations: all Tiers, MDD (continued)

Author, year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
Jorge et al., 2004[130] RCT, primary outcome at 3 weeks (2 weeks of txt, 1 week followup), ITT Failure in current episode not required Tier 1 Fair	**rTMS** (n = 10) High frequency, 10 sessions **Sham** (n = 10) **Concurrent Medications** All antidepressant medications discontinued **Strategy** Switch	**Subgroup** Patients with stroke/cerebral vascular disease **Diagnosis,%** MDD: 85 Minor depression: 15 **Baseline Depression:** HAM-D_{17} rTMS: 20.1 (6.7) Sham: 20.8 (6.0)	**HAM-D_{17}** Response, n (%) rTMS: 3 (30) Sham: 0 (0) *P* = NS Remission, n (%) rTMS: 1 (10) Sham: 0 (0) *P* = NS Change Score rTMS: 7.3 Sham: NR (can be calculated as 2.7) *P* < 0.006 Change,% rTMS: -38 Sham: -13	**Adverse Events** No significant differences in frequency of adverse events between active and sham rTMS groups Neither group reported seizures or propagation of cortical excitability toipsilateral motor cortex

HAM-D_{17} = 17-item Hamilton Depression Scale; ITT = intent-to-treat analysis; MDD = major depressive disorder; mITT = modified intent-to-treat analysis; NR = not reported; NS = not significant; *P* = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Key Question 6: Health-Related Outcomes—Overview

Understanding the burden of affective disorders on the quality of life of patients is an important component to establishing the overall effectiveness of treatment for these disorders. However, quality of life is rarely assessed in this body of literature. Previous ECT studies have associated ECT with a post-treatment quality-of-life improvement that can be maintained from 1 month to 1 year.[61] Very little quality-of-life data following rTMS, VNS, behavioral, or other nonpharmacologic treatments are available.

Numerous psychometric measures exist to assess an individual's level of functioning and execution of daily living activities, which are both health domains that are related to quality of life. The Global Assessment of Functioning (GAF) and the Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) are scales used to determine patients' ability to function in daily life.[131,132] The Medical Outcomes Study 36 Item Short Form (MOS SF-36 or SF-36) is an internationally recognized generic health survey instrument comprised of 36 items in eight independent health domains used to survey the health status of an individual.[133] The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a 16-item questionnaire that uses a self-report measure to obtain the degree of enjoyment and satisfaction of various areas of daily functioning.[134,135] Finally, the Social Adjustment Scale-Self-Report (SAS-SR) work subscale taps a subset of daily activities that may indirectly reflect patients' quality of life.[136]

The following KQ focuses on the comparative benefit of patient-reported health-related outcomes using quality of life measures with TRD (MDD/bipolar and MDD-only). There were no head-to-head (direct) comparisons identified. Four indirect comparison studies were available and assessed general health status and mental and physical functioning. Two studies compared

rTMS versus sham, one study compared VNS versus sham, and one study compared CBT versus control.

For TRD populations (Tier 1), we identified two studies, both in MDD/bipolar mix samples (Table 89), one comparing rTMS versus sham[80] and one comparing VNS versus sham.[98] Both studies suggested greater benefit for rTMS over the control. An additional study compared MDD patients comparing ECT versus ECT plus rTMS.[64]

Table 89. Number of good- and fair-quality studies by TRD tier and diagnostic mix for KQ 6

Comparison	Tier	MDD-only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 2: ≥ 1 treatment failure	1	0
rTMS vs. Sham	Tier 1: ≥ 2 treatment failures	0	1
rTMS vs. Sham	Tier 2: ≥ 1 treatment failure	0	1
VNS vs. Sham	Tier 1: ≥ 2 treatment failures	0	1
CBT vs. Control	Tier 2: ≥ 1 treatment failure	2	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; rTMS = repetetive transcranial magnetic simulation; VNS = vagus nerve stimulation; vs. = versus

Considering additional tiers added two Tier 2 studies of MDD-only populations comparing CBT versus control group[93,94] that showed no difference in outcomes (Table 89). Additionally, a study that compared rTMS to sham is in Tier 2 and suggests an increase in quality of life in the active group using the SF-36 and the Q-LES-Q.[87,115,116,119,124,125] A tier 2 study conducted in 40 patients comparing ECT to rTMS illustrated improvements in quality of life using the GAF.[118]

Strength of Evidence: Tier 1 (TRD)

One study directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes. The study shows no difference in quality of life that compared ECT to ECT plus rTMS.[64] No evidence directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes. Three studies provided indirect evidence. Neither of these two Tier 1 studies assessed quality of life for a nonpharmacologic intervention versus control, instead assessing general health status and mental and physical functioning, and related health domains, for a nonpharmacologic treatment versus sham comparison. One study provided insufficient strength of evidence to assess whether there was a greater improvement in the ability to function following treatment with rTMS compared to sham, as results were mixed (Table 90).[80] Results were in the same direction favoring rTMS, but one of the active arms (low-right rTMS) produced statistically greater improvement than sham, while the second active arm (high-left rTMS) produced greater improvement that did not reach statistical significance. The other study provided low strength of evidence that health status did not differ significantly following treatment with VNS or sham.[98]

Table 90. Strength of Evidence: Health-related outcome measures – Tier 1

Comparison	Number of studies; subjects	Risk of bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. ECT + rTMS	1, 22	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	No difference between groups in improvements to daily functioning Low
rTMS vs. sham	1; 60	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	High-left rTMS produces greater improvement in health status and daily functioning than sham (P = 0.09) Low rTMS produces greater improvement in health status and daily functioning than sham (P = 0.03) Low
VNS vs. sham	1; 214	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	No difference between VNS vs. sham in daily functioning Low

ECT = electroconvulsive therapy; NA = not applicable; P = p-value; RCT = randomized controlled trial; rTMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Key Question 6: Health-Related Outcomes-Key Points

One study directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes (ECT to ECT plus rTMS study).[64]

We identified five relevant studies that compared outcomes related to quality of life for patients who underwent rTMS or VNS versus sham, or CBT compared to a control group. Three studies[87,93,94,115,116,119,124,125] involved patients with MDD-only, and the other two studies[80,98] involved patients with MDD and/or bipolar disorder. The studies were funded by the United States federal government, hospitals, and universities. The active treatment duration across studies ranged from 2 to 16 weeks.

Overall, the study samples were relatively small; two of the four studies had study samples of 50 or fewer patients, but one had a study sample of 491. All studies were RCTs and were rated as fair quality. One study found statistically significant differences in GAF between one active arm and sham, but not between the other active arm and sham.[80] Additionally, two studies reported significant changes ($P < 0.05$) in the SAS-SR work subscale and the SF-36 Mental Component Score and the Q-LES-Q Total Score, respectively.[87,93,115,116,119,124,125]

Key Question 6: Health-Related Outcomes—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1

No Tier 1 data were available for either the MDD-only or MDD/bipolar populations.

Tier 2. Patients With one or More Treatment Failures

MDD-Only

One study compared ECT versus rTMS in 40 patients (Table 91).[59] The study used the GAF to measure changes in functioning in the patients. Though both groups showed improvement from baseline, there were no between group differences in the measure.

Table 91. Quality of life of ECT versus rTMS: Tier 2, MDD

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Grunhaus et al., 2003[59] RCT Did not specify failure in the current episode 4 weeks Fair	**ECT (n = 20)** 35% bilateral, mean sessions 10.25 (SD 3.1) **rTMS (n = 20)** High frequency, 20 sessions (4 weeks)	**Global Assessment of Functioning (GAF)** **Baseline score, mean (SD)** ECT: 39.8 (9.3) rTMS: 48.9 (10.8) **Endpoint score, mean** (SD) ECT: 60.6 (13.5) rTMS: 62.5 (18.8) Group by time interaction, P = NS

ECT = electroconvulsive therapy; NS = not significant; P = p-value; RCT = randomized controlled trial; rTMS = transcranial magnetic stimulation; SD = standard error

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Tier 1. Patients With two or More Treatment Failures

MDD-Only

One study compared ECT and an ECT plus rTMS using the GAF to assess quality of life (Table 92).[64] The intervention groups did not differ significantly on the final score.

MDD/Bipolar

No data available.

Tier 2

No Tier 2 data were available for either the MDD-only or MDD/bipolar populations.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 92. Quality of life of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Pridmore et al., 2000[64] RCT 2 to 4 weeks Did not specify failure in the current episode Fair	**ECT (n = 11)** 100% unilateral, 6 sessions **ECT plus rTMS (n = 11)** ECT: 100% unilateral (day 1), plus high-frequency rTMS: (days 2-5) Repeated in week 2; 8 sessions	**Global Assessment of Functioning** Baseline score, median ECT: 41 ECT plus rTMS: 41 Endpoint (at 2 weeks) score, median (SD) ECT: 70 ECT plus rTMS: 65 Comparison of median difference between groups, *P* = NS

ECT = electroconvulsive therapy; NS = not significant; P = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

MDD-Only

There were no eligible studies.

MDD/Bipolar

One study compared rTMS treatment (two versions—LFR-rTMS and HFL-rTMS) to a sham procedure and found no significant differences between the active rTMS groups compared with the sham group in the GAF mean score change (Table 93).[80] However, they found a statistically significant difference in the GAF mean score change between the LFR-rTMS versus sham groups ($P = 0.03$), though the difference is not clinically significant as all groups remained in the 41–50 point range, which is rated as serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) or any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).[137]

Tier 2: Patients With one or More Treatment Failures

MDD-Only

One study compared rTMS to sham procedure and found significant differences between the two groups in both the SF-36 mental component score ($P = 0.032$) and the Q-LES-Q total score ($P = 0.035$) (Table 94).[87,115,116,119,125,138]These changes are small and their clinical significance is unclear.

MDD/Bipolar

There were no eligible studies.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Vagus Nerve Stimulation Versus Sham

Tier 1. Patients With two or More Treatment Failures

MDD-Only

There were no eligible studies.

MDD/Bipolar

One study compared VNS and a sham procedure using the MOS SF-36 to assess quality of life (Table 95).[98] The intervention and control groups did not differ significantly on either the mental or physical components of the MOS SF-36 instrument.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 93. Quality of life of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Fitzgerald et al., 2003[80] 2 weeks, all reported patients included Did not require failure in the current episode Fair	**High-rTMS (n = 20)** High frequency, 10 sessions **Low-rTMS (n = 20)** Low frequency, 10 sessions **Sham (n = 20)**	**Global Assessment of Functioning** Baseline score, mean **(SD)** High rTMS: 43.0 (6.8) Low rTMS: 43.5 (9.9) Sham: 42.7 (7.1) Endpoint score, mean (SD) At week 2 High rTMS: 45.2 (7.1) Low rTMS: 46.3 (8.5) Sham: 42.5 (6.8) Change, mean At week 2 High rTMS: 2.2 Low rTMS: 1.4 Sham: 0.2 High rTMS vs. sham: *P* = 0.09 Low rTMS vs. sham: *P* = 0.03

n = number; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; VNS = vagus nerve stimulation; vs = versus

Table 94. Quality of life of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
O'Reardon et al., 2007,[87] Janicak et al,2007,[115] and Solvason et al., 2007[116] RCT 6 weeks, all reported patients included Required to have failed at least one in this or most recent episode or four failed attempts in lifetime. Fair	**rTMS (n=155)** High frequency, up to 30 sessions **Sham (n=146)**	**Medical Outcomes Study Short Form-36** Mental Component Score, mean (SD) Baseline score rTMS: 20.4 (8.05) Sham: 20.4 (7.76) Change at week 6 rTMS: 5.7 (12.65) Sham: 2.9 (10.6) *P* = 0.032 Physical Component Score, mean (SD) Baseline score rTMS: 50.5 (11.01) Sham: 48.8 (10.35) Change at week 6 rTMS: 0.1 (7.49) Sham: -0.2 (7.23) *P* = 0.682 **Quality of Life, Enjoyment and Satisfaction Questionnaire –Short Form** Baseline score, mean (SD) rTMS: 37.8 (8.23) Sham: 36.5 (7.87) Endpoint score, mean (SD) At week 6 rTMS: 42.2 (12.28) Sham: 39.0 (10.15) Change, mean At week 6 rTMS: 2.0 (9.24) Sham: 1.3 (9.85) *P* = 0.035

n = number; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Table 95. Quality of life of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Rush et al., 2005[98] 10 weeks Two to six failures in current episode. Fair	**VNS (n = 112)** 10 weeks of VNS therapy with continued medications **Sham (n = 110)** Sham: device implanted but not turned on	**Medical Outcomes Study Short Form-36** Analyzed, n VNS: 107 Sham:107 Physical component, change mean (SD) VNS: -0.9 (8.3) Sham: -1.6 (8.4) *P* = 0.480 Mental component, change mean (SD) VNS: 5.0 (11.6) Sham: 4.0 (10.2) *P* = 0.406

n = number; P = p-value; SD = standard deviation; VNS = vagus nerve stimulation

Cognitive Behavioral Therapy Versus Control

Tier 1

No Tier 1 data were available for either the MDD-only or MDD/bipolar populations.

Tier 2. Patients With one or More Treatment Failures

MDD-Only

The Harley et al. study, rated fair quality, compared patients receiving psychotherapy such as CBT or IPT with a control group using the LIFE-RIFT instrument (Table 96).[93] They found no significant differences between the intervention and control groups. They also used the SAS-SR work subscale as a measure of quality of life, reporting a significant difference ($P < 0.05$) between the psychotherapy group compared with the control group.

A larger study in 491 participants compared three interventions, two forms of psychotherapy used in conjunction with medication and just medication with no psychotherapy.[94] It measured quality of life using LIFE-RIFT and found no differences between the interventions.

MDD/Bipolar

There were no eligible studies.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 96. Quality of life of CBT versus control: Tier 2, MDD

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Harley et al., 2008[93] 16 weeks, all reported patients included Did not require failure in the current episode Fair	CBT [DBT] (n = 10) 16 weekly sessions of dialectical behavior therapy skills training Control (n = 9) Waitlist	Lifework-The Range of Impaired Functioning Tool Change, mean (SD) CBT: -1.3 Control: -0.33 *P* = NS Social Adjustment Scale-Self-Report (SAS-Self Report) work subscale Baseline score, mean (SD) CBT/DBT: 82.50 (21.21) Control: 69.22 (17.95) Endpoint score, mean (SD) CBT/DBT: 65.70 (19.27) Control: 69.56 (17.66) Change, mean CBT/DBT: -16.80 Control: 0.34 *P* < 0.05

Table 96. Quality of life of CBT versus control: Tier 2, MDD (continued)

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Kocsis et al., 2009[94] RCT 12 weeks Fair	CBASP (n=200) Cognitive behavioral analysis system of psychotherapy plus medication; 16-20 sessions BSP (n=195) Brief Supportive Psychotherapy; usual medication; 16-20 sessions No psychoterapy (n=96) Medication only	Life-Rift Sore Baseline score, mean (SD) CBASP: 12.69 (2.96) BSP: 12.71 (3.14) No psychotherapy: 12.64 (3.01) Endpoint score, mean (SD) CBASP: 10.24 (3.25) BSP: 10.73 (3.46) No psychotherapy: 10.96 (3.63) Difference, mean CBASP: 2.45 BSP: 1.98 No psychotherapy: 1.68 No difference between comparisons

BSP = brief supportive psychotherapy; CBASP = cognitive behavioral analysis system of psychotherapy; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; Lifework-RIFT = Lifework-The Range of Impaired Functioning Tool; SD = standard deviation

Discussion

Background

This review from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments—electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy (CBT) or interpersonal psychotherapy —as therapies for patients with treatment-resistant depression (TRD). For one issue (see key questions [KQs] below), we also examined pharmacologic (antidepressant) interventions. The core patient population of interest was patients with major depressive disorder (MDD) who met our definition of TRD: failure to respond following two or more adequate antidepressant trials. We also included studies in which the patient population could include a "mix" of up to 20 percent of patients with bipolar disorder (i.e., 80 percent or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations. In addition, we distinguished between patients for whom treatment was directed at the acute phase of disease and those for whom treatment was intended to maintain remission or to prevent relapse.

We structured our review to focus chiefly on our primary population of interest (MDD patients with TRD) but also considered data from studies that likely had a substantial proportion of TRD patients. We worked with our Technical Expert Panel to identify different tiers of definitions for TRD to use in our analytic strategy:

- **Tier 1** evidence (TRD as defined in this report): studies in which patients specifically had two or more prior treatment failures with medications.
- **Tier 2** evidence: studies in which patients had one or more prior treatment failures.
- **Tier 3** evidence: studies in which the number of prior treatment failures was not specified but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures; this data has probable relevance to TRD. Studies which did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

The focus of each of the six KQs or subquestions is listed below (key distinguished elements in italics).

- KQ 1a. Efficacy of nonpharmacologic interventions for *acute-phase* TRD (depressive severity, response, or remission).
- KQ 1b. Efficacy of nonpharmacologic versus pharmacologic interventions for *acute-phase* TRD (depressive severity, response, or remission), for patients with two or more prior treatment failures.
- KQ 2. Efficacy of nonpharmacologic interventions for *maintaining response or remission* with respect to TRD (e.g., preventing relapse or recurrence).
- KQ 3. Efficacy of nonpharmacologic interventions for *acute-phase* TRD as a function of particular *symptom subtypes* (e.g., catatonia or psychosis).
- KQ 4. Harms of nonpharmacologic interventions (i.e., safety, adverse events, or adherence issues).
- KQ 5. Efficacy or harms of nonpharmacologic treatments for selected patient subgroups defined by sociodemographic characteristics or coexisting conditions.

- KQ 6. Health-related outcomes of nonpharmacologic treatments (e.g., quality of life).

In the discussion below, we comment on findings from direct and indirect evidence for clearly defined TRD (Tier 1); where differences were clinically meaningful, we provide the data also reported in Results. Respectively, these terms refer to head-to-head studies or studies involving a control group of some sort, such as a sham procedure or usual care (treatment as usual). As with Results, we include only studies for which we rated the quality as either good or fair; most studies were of only fair quality.

Finally, we graded the strength of evidence for major outcomes and comparisons for the clearly defined TRD population (Tier 1). Detailed information for data from all three tiers was presented in Results, and the reader can refer to the detailed analysis sections in Results for evidence involving Tier 2 and Tier 3 studies. Below, we comment in text about the strength of evidence for the main findings specifically for TRD. To recap, the four levels of strength of evidence are as follows:

1. **High: High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
2. **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.
3. **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.
4. **Insufficient:** Evidence either is unavailable or does not permit estimation of an effect.

Overview of Main Findings

Summaries of our main findings are found in Table 97 through Table 106. If a specific comparison did not involve a Tier 1 population but did have trials conducted in a Tier 2 and/or Tier 3 population, we have listed it in this table, noted "No eligible studies identified," and added a footnote indicating the presence of at least one such study.

Table 97. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a. comparative efficacy of nonpharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	42	Low	1 fair trial: both ECT and rTMS improved symptom severity but did not differ significantly.
ECT vs. rTMS	Response rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT vs. rTMS	Remission rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT plus rTMS vs. ECT	Change in depressive severity	22	Low	1 fair trial: both ECT and ECT plus rTMS improved symptom severity but did not differ significantly.
ECT plus rTMS vs. ECT	Response rate	0	NA	No eligible studies identified. ‡
ECT plus rTMS vs. ECT	Remission rate	22	Low	1 fair trial: ECT and ECT plus rTMS did not differ significantly.
ECT vs. sham	Change in depressive severity	0	NA	No eligible studies identified. ‡
ECT vs. sham	Response rate	0	NA	No eligible studies identified. ‡

Table 97. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a. comparative efficacy of nonpharmacologic treatments (continued)

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. sham	Remission rate	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Change in depressive severity	497	High	7 trials (3 good, 4 fair): rTMS had a significantly greater decrease in depressive severity than sham. 4 fair trials: rTMS had nonsignificantly greater decrease in depressive severity than sham. 2 fair trials: rTMS had greater decrease than sham but significance NR. 1 fair trial: rTMS did not significantly differ from sham.
rTMS vs. sham	Response rate	471	High	4 trials (3 good, 1 fair): rTMS had a significantly higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly higher response rate than sham. 6 fair trials: rTMS had a higher response rate than sham, but significance NR. 1 fair trial: rTMS did not clearly differ from sham, but significance NR.
rTMS vs. sham	Remission rate	223	Moderate	3 trials (2 good, 1 fair): rTMS had significantly greater remission rate than sham. 2 fair trials: rTMS had a greater remission rate than sham but significance NR.
VNS vs. sham	Change in depressive severity	235	Low	1 good trial: VNS and sham did not differ significantly.
VNS vs. sham	Response rate	235	Low	1 good trial: VNS and sham did not differ significantly.
Psychotherapy vs. control	Change in depressive severity	0	NA	No eligible studies identified. ‡
Psychotherapy vs. control	Response rate	0	NA	No eligible studies identified. ‡
Psychotherapy vs. control	Remission rate	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on the EPC program's modified version of the GRADE system; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 or Tier 3 study addressed this comparison.

Table 98. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 1b. comparative efficacy of nonpharmacologic and pharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. pharmacotherapy	Change in depressive severity	39	Low	1 fair trial: ECT had significantly greater improvement in symptom severity than pharmacotherapy.
ECT vs. pharmacotherapy	Response rate	39	Low	1 fair trial: ECT had significantly greater response rates than pharmacotherapy.
Psychotherapy vs. pharmacotherapy	Change in depressive severity	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Response rate	0	NA	No eligible studies identified. ‡
Psychotherapy vs. pharmacotherapy	Remission rate	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 99. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 2. comparative efficacy for maintaining remission

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Maintenance of remission	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Maintenance of remission	68	Insufficient	3 fair trials: no significant differences in maintenance of remission however, small sample sizes in two of the studies and the presence of a co-intervention in the third study make results difficult to interpret
CBT vs. usual care	Maintenance of remission	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews system; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 100. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 3. comparative efficacy for particular symptom subtypes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 101. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4a. impact of nonpharmacologic interventions on cognitive functioning

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Cognitive functioning	72	Insufficient	1 fair trial and 1 fair cohort study: Some evidence suggests no difference between treatments, whereas some evidence suggests ECT may have deleterious impact on cognitive functioning compared with rTMS (1 study: significant effect on 1-week recall; both studies: nonsignificant effect on all other measures).
ECT vs. ECT + rTMS	Cognitive functioning	22	Insufficient	1 fair trial: no significant differences in a single item measure on memory problems
rTMS vs. sham	Cognitive functioning	101	Insufficient	3 trials (1 good, 2 fair): Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham (2 trials: significant differences in memory, verbal fluency; all other findings nonsignificant or significance not reported)

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.

Table 102. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4b. specific adverse events

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Adverse events	0	NA	No eligible studies identified. ‡
ECT vs. ECT + rTMS	Adverse events	22	Low	1 fair trial: no significant differences in specific adverse events
rTMS vs. sham	Adverse events	68	Low	1 good trial: rTMS resulted in significantly more scalp pain at the stimulation site than sham.
VNS vs. sham	Adverse events	235	Low	1 fair trial: Some differences in specific adverse events reported (*P* = NR)

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus
*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.
†Good and fair designations relate to quality ratings for each study.
‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 103. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4c. withdrawals due to adverse event

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Withdrawals	30	Low	1 fair cohort study: no difference in withdrawals between ECT and rTMS groups (*P* = NR).
ECT vs. sham	Withdrawals	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Withdrawals	277	Insufficient	7 trials (1 good, 6 fair): trials showed mixed results about withdrawals attributed to adverse events.
VNS vs. sham	Withdrawals	235	Low	1 good trial: VNS had greater withdrawals attributed to adverse events than sham (significance NR).
CBT vs. usual care	Withdrawals	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 104. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4d. adherence as measured by overall withdrawals

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Overall withdrawals	72	Low	1 fair trial and 1 fair cohort study: studies showed more withdrawals in ECT group compared with sham (*P* = NR).
ECT vs. sham	Overall withdrawals	0	NA	No eligible studies identified. ‡
rTMS vs. sham	Overall withdrawals	325	Insufficient	8 fair trials: trials showed mixed results about withdrawals.
CBT vs. usual care	Overall withdrawals	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 105. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 5. efficacy and harms for selected populations

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
rTMS vs. sham	Changes in depressive severity	34	Low	1 fair trial: rTMS produced better outcome than sham in young adult population (ages 18–37).
rTMS vs. sham	Changes in depressive severity	20	Low	1 fair trial: rTMS produced better outcome than sham in older adults with post-stroke depression.
rTMS vs. sham	Response	34	Low	1 fair trial: rTMS produces better response rates than sham in young adult population (ages 18–37).
rTMS vs. sham	Response	20	Low	1 fair trial: no difference between rTMS and sham for older adults with post-stroke depression.
rTMS vs. sham	Remission	20	Low	1 fair trial: no difference between rTMS and sham in older adults with post-stroke depression.

rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

Table 106. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 6. health-related outcomes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. ECT + rTMS	Health-related outcomes	22	Low	There were no differences between groups in improvements in daily functioning.
rTMS vs. sham	Health-related outcomes	60	Low	1 fair trail: low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham.
VNS vs. sham	Health-related outcomes	214	Low	1 fair trial: VNS and sham groups did not differ significantly in daily functioning.
CBT/DBT vs. control	Health-related outcomes	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

KQ 1a: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Each Other in TRD Populations (Tier 1)

Direct Evidence

Table 107. Number of Tier 1 (TRD) studies of head-to-head comparisons of nonpharmacologic treatments, by comparison

Comparison	Number
ECT plus rTMS vs. ECT	1
ECT vs. rTMS	1

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD is limited to two fair trials (both in MDD-only populations) (Table 107). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of VNS or psychotherapy with another nonpharmacologic intervention.

Indirect Evidence

We identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS, or psychotherapy, with a control or sham procedure in Tier 1 populations. We identified no eligible ECT versus control studies (Table 108). The number of these trials with the same or similar control group was very small, so we could not pool them quantitatively. We could, however, assess the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

Table 108. Number of Tier 1 (TRD) studies of nonpharmacologic interventions against controls or usual care, by comparison

Intervention and Control	Number
ECT vs. sham	0
rTMS vs. sham procedure	15
VNS plus usual care vs. usual care	1
Psychotherapy plus usual care vs. usual care	0

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than 3 times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham.

In the only other Tier 1 comparison, one good-quality VNS versus sham control trial (a mixed MDD/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

KQ 1b: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Medications in TRD Populations (Tier 1)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) for Tier 1 trials is limited to one fair trial (a mixed MDD/bipolar population). ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71% vs. 28%) than medications (low strength of evidence) (Table 109).

Table 109. Number of Tier 1 (TRD) studies involving pharmacotherapy, by comparison

Intervention	Number
ECT vs. pharmacotherapy	1
CBT vs. pharmacotherapy	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; vs. = versus

Indirect Evidence

Indirect evidence about procedures or psychotherapy (vs. sham or nonpharmacological controls) were presented above as part of KQ 1.

We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, there were no comparable, common control groups not receiving a mood-related medication to allow such comparisons.

Instead, we determined mean average outcomes for pharmacologic treatments.

- For switching strategies, mean pharmacologic response rates averaged 39.8 percent (95% CI, 30.7–48.9) and mean remission rates averaged 22.3 percent (95% CI, 16.2–28.4);
- For augmentation, mean response rates averaged 38.1 percent (95% CI, 31.0–45.3) and mean remission rates average 27.2 percent (95% CI, 20.4–34.0); and
- For maintenance strategies, mean response rates averaged 27.3 percent (95% CI, 19.8–34.8) and mean remission rates averaged 16.8 percent (95% CI, 13.5–20.2).

Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should only be compared to nonpharmacologic outcomes with caution.

KQ 2. Efficacy of Nonpharmacologic Interventions for Maintenance of Remission or Prevention of Relapse in TRD Populations (Tier 1)

Direct Evidence

With respect to maintaining remission (or preventing relapse), there were no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence

Three fair trials compared rTMS with a sham procedure and found no significant differences, however, too few patients were followed during the relapse prevention phases in two of the three studies and patients in the third received a co-intervention providing insufficient evidence for a conclusion. We had no eligible studies for ECT, VNS, or psychotherapy.

KQ 3. Efficacy of Nonpharmacologic Interventions for Patients with Different Symptomatology in TRD Populations (Tier 1)

Direct Evidence

We identified no Tier 1 trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

Indirect Evidence

We identified no studies testing either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

KQ 4. Harms of Nonpharmacologic Interventions in TRD Populations (Tier 1)

Direct Evidence

In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients, however the data were insufficient to reach a conclusive result. For just this set of analyses, we examined both trials and cohort studies, and we focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

Cognitive Functioning

For Tier 1 studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence).

No differences between groups on a single item measure of cognitive functioning were found in a study comparing ECT with ECT and rTMS (insufficient strength of evidence).

Specific Adverse Events

One Tier 1 study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence).

Withdrawals

We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).

Evidence for ECT compared with rTMS indicated higher rates of overall withdrawals in the ECT compared to the rTMS group (*P* = NR; low strength of evidence).

Indirect Evidence

We attempted to include data from the same types of studies and for the same outcomes as for direct evidence. We identified no studies comparing ECT versus control.

Cognitive Functioning

Mixed evidence on cognitive functioning in rTMS versus sham was insufficient to draw a conclusion (insufficient strength of evidence).

Specific Adverse Events

rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence).

Some differences in the frequency of specific adverse events were seen when comparing VNS and sham groups, but the significance of the findings was not reported (low strength of evidence).

Withdrawals

Findings were mixed in Tier 1 studies as to whether rTMS groups had greater rates of withdrawals due to adverse events and overall withdrawals than groups receiving sham procedures (insufficient evidence for both).

There was low strength of evidence that there were greater withdrawals due to adverse events in the vagus nerve stimulation group compared to sham.

No Tier 1 studies reported on withdrawals for CBT groups versus those receiving some form of usual care.

KQ 5. Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups in TRD Populations (Tier 1)

Direct Evidence

We found no studies (in any tier) directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

Indirect Evidence

Three Tier 1 trials compared rTMS versus sham. A single trial, each, found that rTMs produced a greater decrease in depressive severity than sham for young adults (ages 18–37) and in older adults with post-stroke depression (both low strength of evidence). A single trial in young adults indicated that rTMS produces a greater response rate than sham in young adults (ages 18–37) (low strength of evidence), while a single study identified no difference in response rates between rTMS and sham in older adults with post-stroke depression (low strength of evidence). Finally, a single study found no difference in remission rates for rTMS versus sham in older adults with post-stroke depression.

KQ 6. Health-Related Outcomes of Nonpharmacologic Treatments in TRD Populations (Tier 1)

Direct Evidence

With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

Indirect Evidence

Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

Applicability

For the limited amount and low strength of evidence available, the data for Tier 1 (TRD) is generally applicable to TRD populations. Populations enrolled in these trials appeared representative of our target population. Studied interventions were comparable to those in routine use, though dose and duration of nonpharmacologic treatment often varied between studies. Measured outcomes on the whole reflected the most important clinical outcomes for depression measures, although reporting was inconsistent; outcomes for the other key questions were much more restricted. Followup periods were generally shorter than desirable, but most were sufficient to measure an initial acute-phase treatment response. Study settings were a mixture of inpatient and outpatient. Some evidence highlights the importance of patient acceptability of treatment as some patients refuse particular interventions. An individualized balance between patient's needs and concerns must be taken into account during selection from a range of nonpharmacologic and pharmacologic antidepressant treatment options. The use of varying definitions of TRD in the trials and the absence of analyses considering the effect of the number of current episode treatment failures on outcomes hindered interpretation of data, leading to the use of a tiered system. The evidence base combining data for Tiers 1–3 on the whole produced findings that were consistent with Tier 1 TRD data and also appear applicable to TRD populations.

Limitations of the Evidence Base

Lack of use of a Standard Definition of TRD

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by variable definitions of TRD. Although these definitions appear to be consolidating towards a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it. Use of multiple definitions makes synthesis of the available information difficult, as the effect of combining patients with one treatment failure with those of two or more (or four or more) remains unclear.

Similarly, the failure of studies to describe the number of treatment failures prevented us from being able to stratify our outcomes by the number of failed trials within Tier 1 studies and assess the role of number of failures in TRD on outcomes.

Ultimately, TRD is a complex phenomenon that encompasses the number of treatment failures, the adequacy of prior treatments, depressive severity, comorbidities (both psychiatric and medical), symptom subtypes, and chronicity. The currently available evidence base has yet to successfully and consistently apply a standard definition.

Failure to Consistently Assess Number of Failures in Current Episode

Given the difficulty in accurately assessing adequacy of prior treatment trials over a lifetime, a history of failed treatment attempts in a current episode is likely a more accurate measure of treatment resistance. It is likely that many of those who reported lifetime histories of two or more failures did have them in the current episode, but few studies required such a failure in their selection criteria; many studies may be mixing current failure with more chronic failures.

Few Head-to-Head Studies of Nonpharmacologic Intervention

The small number of existing head-to-head studies limits the strength of all our findings to either low or insufficient evidence, making firm conclusions about comparative effectiveness

impossible. Only two studies occurred in our main population of interest: patients with MDD who had two or more antidepressant failures.[58,64]

Heterogeneity of the Populations (MDD and MDD/Bipolar mix)

This mixture of diagnostic disorders in samples made interpretation of the data difficult. Populations studied included MDD and MDD/bipolar mix patients. We selected a 20 percent cutoff to decrease the likelihood of the mix affecting outcomes (e.g., in a study of 40 patients, if 8 had bipolar disorder and were roughly evenly distributed between treatment arms, their outcomes would need to be extreme to substantially affect outcome). This need to clarify a specific cutoff, however, excluded studies that may have had relevant populations. Further, because results were not stratified by MDD and bipolar disease, the precision of the effect on the nonpharmacologic outcomes may have been distorted.

Failure to Consider a Spectrum of Depressive Severity

Most patients involved in studies were severely depressed and analyses did not assess how the degree of depression along the severity spectrum may affect outcomes in comparative studies. For example, the most severely depressed may have different outcomes with one versus another intervention than those who are severely depressed but to a lesser degree.

Heterogeneity of Interventions and Intervention Strategies

The literature is characterized by a large variety of treatment strategies used (augmentation, switch, a combination of the two), a wide variety of treatment parameters used (length and dose of ECT, number of rTMS sessions), and variable and uncontrolled use of psychotropic medications, all of which make interpretation and synthesis of the studies difficult.

Limited outcome elements assessed. Although they reported one or two of the pertinent outcomes, the majority of the relevant studies did not assess both response and remission rates. These measures are especially important to allow a clinically meaningful interpretation of findings.

Few Comparisons of Nonpharmacologic to Pharmacologic Treatments in TRD Patients

For many clinicians, the next step following failure of two antidepressant treatments is not consideration of a nonpharmacologic treatment but usually consideration of a different pharmacologic strategy. The role of nonpharmacologic interventions in the sequence of treatment choices remains unclear.

Difficulty in Identifying a Reasonable Sham Control Group for Device-Related Studies

Challenges in finding an appropriate sham arm may have distorted results from the intervention-control comparisons. Because of the need for general anesthesia, “sham ECT” has proven ethically problematic over the years. Given the noninvasive nature of rTMS, there is much objection to the use of a sham control condition, in which the electrode would be placed against the scalp but the magnetic stimulation not applied. The problem is that a completely “inert” sham condition experience may not be credible to patients who are aware of the noise and vibration that typically accompanies active rTMS.[53,139] Similarly, the limited number of reported

VNS studies identified have come under similar criticism for the apparently transparent nature of the control condition.[140]

Inadequate Study Design to Assess Longer Term Outcomes

Studies need to have more long-term monitoring over time so that the outcomes can be further studied. For example, the available studies for ECT did not follow patients long enough to assess potential cumulative effects on cognitive functioning that may distinguish it from other interventions. Additionally, longer monitoring periods are necessary to compare the maintenance of remission.

Studies Were not Designed to Answer Many of the Outcomes Relevant to the KQ

Outcomes such as relapse, cognitive functioning, adverse events, withdrawal due to adverse events, and health-related outcomes are not often primary outcomes, limiting the power to adequately test hypotheses about such differences between nonpharmacologic interventions.

Absence of Psychotherapy Studies Involving a TRD Population

Although some Tier 2 and 3 studies involved psychotherapy, there were no studies addressing a Tier 1 population (TRD). Also, no studies from any tiers involved interpersonal therapy. While there are a variety of reasons that make clinical trials involving psychotherapy challenging (e.g., treatments are often not widely available outside research centers, and both patients and clinicians often view these studies as underpowered or the research protocol as too complicated for application in practice settings), such research would be quite informative for decisionmakers.

These Treatments are Quite Different

Differences in these interventions—how long it takes to reach an adequate dose, how effectively patients can be blinded, how long it takes to obtain a response, how long the results last—make it challenging to directly compare these varying treatments. For example, with ECT, if there is no effect in 2 weeks, one might consider switching treatments, whereas with CBT, such a latency would not be a cause for concern.

Limitations of This Review

This area of comparative clinical research is in its infancy, and few relevant trials were available. The paucity of data limited our ability to pool findings statistically. Specifically, we were not able to quantitatively synthesize data from head-to-head comparisons, nor were we able to indirectly compare the nonpharmacologic literature by pooling data from studies sharing equivalent control groups. Our synthesis, then, is primarily qualitative.

The dearth of relevant trials also prevented us from assessing whether key elements might suggest one nonpharmacologic treatment over another. In particular, we were unable to assess what the effect on outcome was of key, clinically relevant elements of interest: population variables (MDD and MDD/bipolar mix; varying depressive severity; and requiring treatment failures to be in the current episode) and intervention variables (using an augmentation versus switch treatment strategy; varying by nonpharmacologic treatment characteristics).

Future Research

This area of comparative clinical research is in its infancy. Key areas for future research need primarily to lay more robust foundations for an evidence base that can better inform decisions for clinicians and patients.

The Field Needs a Standard Definition of TRD That Investigators Should use in Their Clinical Trials Research

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by the variability in TRD definitions. Although these definitions appear to be converging on a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it. Progress in this area of research requires better standardization of this concept, so that future reviews of the evidence do not need to resort to differentiating, as we did, between "Tier 1" studies (i.e., TRD by this definition based on two or more treatment failures) and "Tier 2 or 3" types of studies. The latter do provide information that helps illuminate likely impacts of these interventions on patients with TRD, but that is not the same thing as having robust studies focused clearly on the patient population of greatest interest. The challenge will be to provide a definition that operationalizes TRD to make it feasible for clinicians while at the same time successfully capturing the complexity of treatment resistance.

More Clinical Trials, as Well as Other Possible Study Designs, That Compare Nonpharmacologic Interventions With Other Nonpharmacologic Options and With Pharmacologic Treatments are Necessary to Inform Decisionmaking in TRD

Clinicians, patients, and policymakers need additional relevant data to guide difficult treatment decisions about what to do next: try another medication trial (and should it be an augmentation, switch, or combination strategy?); add (or switch to) rTMS, ECT, VNS, or psychotherapy?

Also, given that treatment options for many TRD patients include medications, trials should directly compare nonpharmacologic interventions with each other and with pharmacologic treatments.

The Number of Treatment Failures in the Current Episode Should be Delineated Carefully

This information, more likely to be accurate than lifetime histories of failures, can help investigators determine whether the particular number of failures, or reaching a particular number of failures in a current episode, can help differentiate between nonpharmacologic treatment choices. For example, for patients with two failures in a current episode, the outcomes may not differ between cognitive therapy and rTMS; however, for patients with a different (higher or lower) number of failures in the current episode, one nonpharmacologic treatment may indeed be better than the other. Currently, we do not know what the proper threshold is for selection of treatment. Clarification of the scientific basis for such a decision would substantially improve decisionmaking.

Clarifying Whether Responses Differ for TRD Patients With MDD Compared to Those With Bipolar Disorder Will Help to Guide Future Clinical Trial Design

Our decision to include trials with patient populations including up to 20 percent with bipolar disorder (i.e., the "mixed" populations noted earlier) was guided by clinical experience and common sense but not by data. Testing to see whether outcomes differ between the two groups can yield information about inclusion criteria (should the mix be 0%, 10%, 20%, etc.?) that may be useful to investigators in designing TRD trials and may be important to consider as a potential covariate in analyses involving such mixes.

Greater Consideration Should be Given to the Role That the Spectrum of Depressive Severity Plays

Using a finer gradation of depressive severity than investigators now typically employ might identify whether particularly severe degrees of depression, most commonly understood currently as a HAM-$D_{17} \geq 20$, may respond differently to the available nonpharmacologic interventions than do less severe levels of depression. These gradations may lead clinicians to a better understanding of severe depression and its role in guiding treatment selection in TRD.

Direct Comparisons of Treatment Strategies, Holding Consistent any Coexisting or Concomitant Therapies, are Imperative

Decisionmakers need to know whether outcomes with nonpharmacologic treatments are better when such a treatment augments the current treatment, replaces the current treatment, or replaces the current treatment in combination with another treatment. When ongoing treatment is uncontrolled and reflects a variety of treatments—e.g., some patients continue with atypical antipsychotics, some with mood stabilizers, some with no psychotropic medications—results of such studies are difficult, if not impossible, to interpret.

Consistent Reporting of Changes in Depressive Severity, Response Rates, and Remission Rates is Crucial

To allow for better comparisons of clinical outcomes in this difficult-to-treat population, all three measures offer useful information for clinicians. Thus, for either trials or observational studies, investigators should attempt to collect data on all three routinely.

Application of Consistent, Accepted Protocols in Trials is Necessary

Making sure that patients receive equivalent doses of different nonpharmacologic interventions is more difficult than making sure of this for pharmacologic interventions. Nevertheless, investigators designing trials of nonpharmacologic therapies can attempt to do so by implementing standard accepted protocols for their trials. Such "dosing" had been difficult to control when that protocol was in the process of being developed, as with rTMS, but given current treatment parameters, this standardization is a goal well worth trying to reach.

More Careful and Consistent Assessment of Adverse Events is Required

Adverse event reporting is quite limited and over a short timespan, and what exists is variable and inconsistent. Systematic collection and more consistent reporting of data on harms—i.e., adverse events and negative side effects—and information about attrition and withdrawal would provide useful information to help balance information now focused on clinical benefits. Use of the CONSORT (Consolidated Standards of Reporting Trials) statement (available at: http://www.consort-statement.org/home/), which guides proper reporting of study information (including the presentation of adverse events), would strengthen reporting both harms and other clinical trial findings; it would also aid in the critical appraisal and interpretation of all study results. Further, a more informative assessment of adverse events would require studies to be able to assess long-term and cumulative outcomes.

Including key Relevant Measures and Subgroups in Subsequent Research is Desirable

As indicated by the review, nearly no evidence exists on how the effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristic (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression; perinatal depression). Also essentially missing is information about health-related outcomes, especially those reported by patients, that concern their quality of life or levels of functional impairment. Subsequent studies should focus on employing known, reliable, and valid measures of patient-reported outcomes, such as the MOS SF-36,[141] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[135] and the EQ-5D.[142]

Including Comparisons of Newer Nonpharmacologic Interventions Will be Important in Future Research

As new nonpharmacologic treatments are developed and tested, investigators should try to include them as potential comparators. At the time we started this comparative effectiveness review, clinical trial data on some of the developing nonpharmacologic interventions, such as magnetic seizure therapy,[143-145] deep brain stimulation,[146-148] or mindfulness-based cognitive therapy[149] were insufficient (from the published literature) for us to try to include them. As the evidence bases grow to support the efficacy of such additional nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs.

Conclusion

Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS; however, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for comparative benefits. Specifically, there was low strength of evidence that ECT and rTMS did not produce different clinical outcomes in TRD, and low strength of evidence that ECT produced better outcomes than pharmacotherapy. No trials

directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions to one another and to pharmacologic treatments, and to carefully delineate the number of adequate treatment failures in the current episode.

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Appendix A. Search Strategy

TRD Search 06.23.09

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	110342
#2	Search #1 Limits: Entrez Date from 1980/01/01, Humans, English, All Adult: 19+ years	56274
#3	Search #2 Limits: Editorial, Letter, Case Reports	7200
#5	Search "Case Control Studies"[Mesh]	421177
#6	Search #2 AND #5	3156
#7	Search #3 OR #6	10272
#8	Search #2 NOT #7	**46002**
	Depression articles limited to English, Human, and Adults, with no editorials, letters, case reports or case-control studies.	
#9	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	123383
#10	Search #8 AND #9	2910
#11	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	379438
#12	Search #10 AND #11	**48**
	48 Psychotherapy/CBT/Depression articles limited to the "refractory" terms.	
#13	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	10514
#14	Search #8 AND #13	1112
#16	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] **These are the terms used for RCTs.**	392864
#17	Search #14 AND #16	203
	There are 203 RCTs about Depression and ECT.	
#18	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	1992678
#19	Search #14 AND #18	361
	There are 361 "observational studies" about Depression and ECT.	
#20	Search #17 OR #19	**447**
	Combining the RCTs and Observational studies for the ECT literature here.	
#21	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	2864
#22	Search #8 AND #21	**141**
	141 TMS articles.	
#23	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	808
#24	Search #8 AND #23	**37**
	37 VNS articles.	
#25	Search #12 OR #20 OR #22 OR #24	**649**
	Combining all results for the main search here: Psychotherapy, ECT, TMS, and VNS.	

Final number of records after duplicates removed

630

A search with analogous terms was performed in the following databases:

Embase = **269 (159 after duplicates removed)**
PsycINFO= **422 (296 after duplicates removed)**
Cochrane = 6 (no duplicates found)
EndNote file for the main search = 1346 (1074 after duplicates removed)

TRD Update Search 11.18.2010

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	120871
#2	Search ((#1) AND "2009/04/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	9152
#3	Search #2 Limits: Editorial, Letter, Case Reports	909
#4	Search "Case Control Studies"[Mesh]	476252
#5	Search #2 AND #4	558
#6	Search #3 OR #5	1460
#7	Search #2 NOT #6	7692
#8	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	131504
#9	Search #7 AND #8	758
#10	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	414955
#11	Search #9 AND #10	25
#12	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	11003
#13	Search #2 AND #12	149
#14	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	431969
#15	Search #13 AND #14	21
#16	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	2109685
#17	Search #13 AND #16	27
#18	Search #15 OR #17	37
#19	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	3733
#20	Search #2 AND #19	78
#21	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	988
#22	Search #2 AND #21	18
#23	Search #22 OR #20 OR #18 OR #11	143
#24	Search #23 Limits: Humans, English, All Adult: 19+ years Sort by: PublicationDate	77
#25	Search #23	143

A search with analogous terms was performed in the following databases:

PubMed 76 (77 before duplicates removed)
Embase 80 (187 before duplicates removed)
PsycINFO 170 (211 before duplicates removed)
The Cochrane Library 26 (27 before duplicates removed)
EndNote file for the Update Search = 352 (before being added to main database and duplicates removed)

TRD Pharmacologic Search (Key Question 1b)

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents"[MeSH]	37171
#2	Search "Fluoxetine"[Mesh] OR "Sertraline"[Mesh] OR "Paroxetine"[Mesh] OR "Citalopram"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "nefazodone "[Substance Name] OR "mirtazapine "[Substance Name] OR "venlafaxine "[Substance Name] OR "desmethylcitalopram "[Substance Name] OR Escitalopram[tw] OR "duloxetine "[Substance Name] OR "Trazodone"[Mesh] OR "O-desmethylvenlafaxine "[Substance Name] OR "Imipramine"[Mesh] OR "Desipramine"[Mesh] OR "Nortriptyline"[Mesh] OR "Amitriptyline"[Mesh] OR "Phenelzine"[Mesh] OR "Tranylcypromine"[Mesh] OR "Doxepin"[Mesh] OR "Clomipramine"[Mesh] OR "Maprotiline"[Mesh]	39294
#3	Search Fluoxetine OR Sertraline OR Paroxetine OR Citalopram OR Fluvoxamine OR Bupropion OR Nefazodone OR Mirtazapine OR Venlafaxine OR Escitalopram OR Duloxetine OR Trazodone OR Desvenlafaxine OR Imipramine OR Desipramine OR Nortriptyline OR Amitriptyline OR Phenelzine OR Tranylcypromine OR Doxepin OR Clomipramine OR Maprotiline	48657
#4	Search #1 OR #2 OR #3	70932
#5	Search ("Depression"[MeSH] or "Depressive Disorder"[MeSH])	113094
#6	Search "Drug Resistance"[MeSH] OR refractory[tw] OR resistant[tw]	387599
#7	Search #4 AND #5 AND #6	1359
#8	Search ("1980"[Entrez Date] : "3000"[Entrez Date]) AND (#7) Limits: Humans, English	1075
#9	Search #8 Limits: Editorial, Letter, Case Reports	222
#10	Search #8 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	105
#11	Search #8 NOT(#9 OR #10) Sort by: Title	758
	Final number of records after duplicates removed (in comparison with the main TRD nonpharmacologic database).	663

A search with analogous terms was performed in the following databases:

EMBASE (unduplicated) = 78

PsycINFO (unduplicated)= 171

Unduplicated EndNote file for the main search = 912

TRD Pharmacologic Search (KQ1b) 11.19.2010

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents"[MeSH]	39236
#2	Search "Fluoxetine"[Mesh] OR "Sertraline"[Mesh] OR "Paroxetine"[Mesh] OR "Citalopram"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "nefazodone "[Substance Name] OR "mirtazapine "[Substance Name] OR "venlafaxine "[Substance Name] OR "desmethylcitalopram "[Substance Name] OR Escitalopram[tw] OR "duloxetine "[Substance Name] OR "Trazodone"[Mesh] OR "O-desmethylvenlafaxine "[Substance Name] OR "Imipramine"[Mesh] OR "Desipramine"[Mesh] OR "Nortriptyline"[Mesh] OR "Amitriptyline"[Mesh] OR "Phenelzine"[Mesh] OR "Tranylcypromine"[Mesh] OR "Doxepin"[Mesh] OR "Clomipramine"[Mesh] OR "Maprotiline"[Mesh]	40799
#3	Search Fluoxetine OR Sertraline OR Paroxetine OR Citalopram OR Fluvoxamine OR Bupropion OR Nefazodone OR Mirtazapine OR Venlafaxine OR Escitalopram OR Duloxetine OR Trazodone OR Desvenlafaxine OR Imipramine OR Desipramine OR Nortriptyline OR Amitriptyline OR Phenelzine OR Tranylcypromine OR Doxepin OR Clomipramine OR Maprotiline	50880
#4	Search #1 OR #2 OR #3	74378
#5	Search ("Depression"[MeSH] or "Depressive Disorder"[MeSH])	120871
#6	Search "Drug Resistance"[MeSH] OR refractory[tw] OR resistant[tw]	415078
#7	Search #4 AND #5 AND #6	1465
#8	Search ((#7) AND "2009/09/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	78
#9	Search #8 Limits: Editorial, Letter, Case Reports	8
#10	Search #8 NOT #9	70
#11	Search #10 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	7
#12	Search #10 NOT #11	63
#13	Search ("Amoxapine"[Mesh] OR "Protriptyline"[Mesh]) OR "Selegiline"[Mesh]	2578
#14	Search "Amoxapine" OR "Protriptyline" OR "Selegiline"	3228
#15	Search #13 OR #14	3228
#16	Search #15 AND #5 AND #6	16
#17	Search #16 Limits: Editorial, Letter, Case Reports	7
#18	Search #16 NOT #17	9
#19	Search #18 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	0
#20	Search #12 OR #18	72
#21	Search #20 Limits: Humans, English	60

A search with analogous terms was performed in the following databases:

PubMed 60 (60 before duplicates removed)
Embase 131 (172 before duplicates removed)
PsycINFO 51 (69 before duplicates removed)
The Cochrane Library 66 (73 before duplicates removed)
EndNote file for the Update Search = 308 (before being added to the main EndNote Database and duplicates removed)

Appendix B. Data Abstraction Forms and Quality Rating Criteria

Inclusion/Exclusion Criteria for Abstract Review

1. Original research (no review articles, editorials, letters to the editor) published in English?

- ◯ Yes
- ◯ No
- ◯ Cannot determine

2. Study was conducted in adult patients with treatment resistant depression (two or more failed prior adequate trials of an evidence-based intervention) and compares at least one of the following interventions with another, a pharmacological intervention or placebo (check all that apply):

- ☐ A - Electroconvulsive Therapy (ECT)
- ☐ B - Repetitive Transcranial Magnetic Stimulation (rTMS)
- ☐ C - Vagus Nerve Stimulation
- ☐ D - Psychotherapy such as Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT)
- ☐ E - Placebo
- ☐ F - Pharmacological intervention
- ☐ G - Deep Brain Stimulation
- ☐ H - Magnetic Seizure Therapy
- ☐ I - Other? _____
- ☐ J - Cannot determine
- ☐ K - None of the above (i.e. not adults, not TRD, not a relevant intervention)

3. (Only answer this if you chose K in the above question, otherwise skip #3)
Has no comparison but is in adults with TRD, examining one of the nonpharmacological interventions, for example it is a case series looking at 40 recipients of magnetic seizure therapy?

- ◯ Yes
- ◯ No

4. Addresses one or more of the following key questions (check all that apply):

- ☐ KQ1 For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), or an evidence-based psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- ☐ KQ2- For adults with TRD, do non-pharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?
- ☐ KQ3 Do non-pharmacologic interventions (single or combination) differ in their efficacy or

effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic (frozen or hyper) or psychotic symptoms)?

☐ KQ4 For adults with treatment-resistant depression, do non-pharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to: amnesia, memory loss, headaches, post-operative complications.

☐ KQ5 How does the efficacy, effectiveness, or harms of treatment with non-pharmacologic treatments for treatment-resistant depression differ for subpopulations?

☐ KQ6 For adults with treatment-resistant depression, do non-pharmacologic interventions differ in regards to other health-related outcomes (e.g., quality of life)?

☐ Cannot determine

☐ None of the above

5. Study design is one of the following:

☐ RCT

☐ Systematic review (Qualitative or quantitative)

☐ Observational Study

☐ Other?

☐ Cannot determine

☐ Case series (no comparison arm)

6. Use for background ? (If Yes, check and flag article)

◯ Yes

◯ No

Inclusion/Exclusion Criteria for Full Text Review

1. Should the article be excluded for any of the following reasons?

☐ Study reported only in abstract (Full text is not available)

☐ Background article

☐ Wrong outcome (i.e. not validated tool, pharmacokinetic or other intermediate outcomes)

☐ Wrong intervention

☐ No relevant comparison and no report of adverse events, harms or adherence

☐ No relevant comparison BUT reports of adverse events, harms or adherence

☐ Wrong population (For example no pediatric or perinatal studies or patients not TRD or analysis does not break out patients with TRD)

☐ Wrong publication type (e.g. letter or editorial)

☐ Other? (Please explain!)

☐ None of the above- should be included!

2. Addresses one or more of the following key questions (check all that apply):

☐ KQ1 For adults with depression , do non-pharmacologic interventions such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), or an evidence-based psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

☐ KQ2- For adults with depression, do non-pharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

☐ KQ3 Do non-pharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating depression as a function of particular symptom subtypes (e.g., catatonic (frozen or hyper) or psychotic symptoms)?

☐ KQ4 For adults with depression, do non-pharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to: amnesia, memory loss, headaches, post-operative complications.

☐ KQ5 How do the efficacy, effectiveness, or harms of treatment with non-pharmacologic treatments for depression differ for subpopulations?

☐ KQ6 For adults with depression, do non-pharmacologic interventions differ in regards to other health-related outcomes (e.g., quality of life)?

☐ Cannot determine

☐ None of the above

3. Study population has previously been treated

☐ Two or more treatments for depression

☐ One or more treatments for depression

☐ No previous treatments for depression

☐ Not reported but referred to as TRD or refractory

☐ Other? (Please explain)

4. Study design is one of the following:

☐ RCT

☐ Systematic review (Qualitative or quantitative)

- [ ] Observational Study
- [ ] Other?
- [ ] Cannot determine
- [ ] Case series (no comparison arm)

Internal Validity Quality Forms

Quality for Experimental Studies

1. Randomization adequate?

- [ ] Yes
- [ ] No
- [ ] Not randomized
- [ ] Method not reported

2. Allocation concealment adequate?

- [ ] Yes
- [ ] No
- [ ] Not randomized
- [ ] Method not reported

3. Was the sample size sufficient to detect appropriate changes in the outcomes of interest? (i.e. was there an explanation of the statistical power?)

- [ ] Yes
- [ ] No

4. Groups similar at baseline?

- [ ] Yes
- [ ] No

5. Outcome assessors masked?

- [ ] Yes
- [ ] No
- [ ] Yes, but method not described
- [ ] Not reported

6. Care provider masked?

- [ ] Yes
- [ ] No
- [ ] Yes, but method not described

☐ Not reported

7. Patient masked?

☐ Yes

☐ No

☐ Yes, but method not described

☐ Not reported

8. Overall attrition high (≥ 20%)?

☐ Yes (please state how high) ____

☐ No

9. Differential attrition high (≥ 15%)?

☐ Yes (please state difference) ____

☐ No

10. Was the statistical analysis based on intention-to-treat (ITT)?

☐ Yes

☐ No

☐ Cannot tell

11. Were outcome measures valid, reliable, and equally applied?

☐ Yes

☐ No

12. Were there any post-randomization exclusions?

☐ Yes (how many?) ____

☐ No

☐ Cannot tell

13. Methods of adverse effects assessment

☐ Patient reported

☐ Physical exam at study visits

☐ Lab evaluations

☐ Standardized scale (e.g. WHO, UKU-SES)

☐ other (please specify) ____

☐ Not applicable

14. Adverse events pre-specified and defined?

☐ Yes

- [ ] No
- [ ] Not applicable

15. Ascertainment techniques for detecting adverse events non-biased and adequately described?

- [ ] Yes
- [ ] No
- [ ] Not applicable

16. Quality rating for experimental study (RCT)

- [ ] Good
- [ ] Fair
- [ ] Poor

If poor, why? _____

Quality Review for Observational Studies

1. Were both groups selected from the same source population?

- [ ] Yes
- [ ] No
- [ ] Yes, but method not described
- [ ] Not reported

2. Did both groups have the same risk of having the outcome of interest at baseline?

- [ ] Yes
- [ ] No
- [ ] Not reported
- [ ] Not applicable

3. Were subjects in both groups recruited over the same time period?

- [ ] Yes
- [ ] No
- [ ] Yes, but method not described
- [ ] Not reported
- [ ] Not applicable

4. Were measurement methods adequate and equally applied to both groups?

- [ ] Yes
- [ ] No
- [ ] Not reported

☐ Not applicable

5. Does the analysis control for baseline differences?

☐ Yes

☐ No

☐ Not applicable

6. Were important potential confounding and modifying variables taken into account in the design and analysis (i.e. through matching, stratification, or statistical adjustment)?

☐ Yes

☐ No

☐ Not applicable

7. Were the statistical methods used to assess the abstracted outcomes appropriate?

☐ Yes

☐ No

☐ Not applicable

8. Was the sample size sufficient to detect appropriate changes in the outcomes of interest? (i.e. was there an explanation of the statistical power?)

☐ Yes

☐ No

9. Was an attempt made to blind the outcome assessors?

☐ Yes

☐ No

☐ Yes, but method not described

☐ Not reported

☐ Not applicable

10. Was the time of follow-up equal in both groups?

☐ Yes

☐ No

☐ Not reported

☐ Not applicable

11. Overall attrition high (≥ 20%)?

☐ Yes (please state how high)

☐ No

12. Differential attrition high (≥ 15%)?

☐ Yes (please state difference)

- [ ] No
- [ ] Not applicable

13. Methods of adverse effects assessment

- [ ] Patient reported
- [ ] Physical exam at study visits
- [ ] Lab evaluations
- [ ] Standardized scale (e.g. WHO, UKU-SES)
- [ ] other (please specify)
- [ ] Not applicable

14. Adverse events pre-specified and defined?

- [ ] Yes
- [ ] No
- [ ] Not applicable

15. Ascertainment techniques for detecting adverse events non-biased and adequately described?

- [ ] Yes
- [ ] No
- [ ] Not applicable

16. Quality rating for observational study?

- [ ] Good
- [ ] Fair
- [ ] Poor - why?

Appendix C. Excluded Studies

No or Wrong Comparison

1. Abbass AA. Intensiveshort-term dynamic psychotherapy of treatment-resistant depression: a pilot study. Depress Anxiety. 2006;23(7):449-52.
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15. Bean GJ, Marchese V, Martin BA. Electric stimulus energy and the clinical response to electroconvulsive therapy. Can J Psychiatry. 1991 Nov;36(9):637-44.
16. Beasley CM, Jr., Sayler ME, Cunningham GE, Weiss AM, Masica DN. Fluoxetine in tricyclic refractory major depressive disorder. J Affect Disord. 1990 Nov;20(3):193-200.

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18. Beutler LE, Engle D, Mohr D, Daldrup RJ, Bergan J, Meredith K, et al. Predictors of differential response to cognitive, experiential, and self-directed psychotherapeutic procedures. J Consult Clin Psychol. 1991 Apr;59(2):333-40.

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Wrong Intervention

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Appendix D. Evidence Tables

Evidence Table 1. KQ1 head to head: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Pridmore, 2000[1] *Country, Setting* Australia, University of Tasmania, Psychological Medicine, Royal Hobart Hospital, inpatient and outpatient *Funding* NR *Research Objective* To determine whether rTMS treatments could be substituted for ECT treatments in a course of ECT, without loss of antidepressant effect, and without increase in subjective side-effects. *Quality Rating* Fair	*Study Design* RCT *Type of Analysis* ITT *N* 22 *Duration* Primary outcome after 2 weeks of txt Interventions G1: ECT Only G2: ECT + rTMS *Medications Allowed* Pts taking antidepressants or mood stabilizers were allowed to continue on these. Not all patients were taking medication at entry. All other psychotropics were ceased 1 week prior to txt initiation *Parameters* ECT: • % receiving bilateral: 0 • Intensity: percentage of 504mC equivalent to age of patient.	*TRD Definition* • 2+ failed ADs from 2+ drug classes (after 1+ month trials at the max manufacturer recommended dose) • Not required to be in current episode *Tier 1* *Inclusion Criteria* • MDD DSM-IV • Right- handed • Age 25-70 • Physically well and • free of epilepsy and intracranial metal objects • exceed both 26 on MADRS and 18 on HAM-D17 *Exclusion Criteria* NR	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD Age, median yrs G1: 47.1 (48) G2: 44.0 (46) Sex, % females G1: 54.5% G2: 45.4% *Right Handed, %* 100% *HAM-D 17* Baseline n G1: 11 G2: 11 Baseline score, median (SD) G1: 30 G2: 28 *MADRS* Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 40 G2: 40	*HAM-D 17* Endpoint score, median (SD) At week 1 G1: 14 G2: 15 At week 2 G1: 7 G2: 8 Change, mean (SD) At week 1 G1: -16 G2: -13' *P* = 0.3 At week 2 G1: -23 G2: -20 *P* = 0.6 Remission HAM-D17<9 G1: 6 (54.5%) G2: 6 (54.5%) *P* = NR *MADRS* Endpoint score, mean (SD)	*Quality of Life* Global Assessment of Functioning (GAF) Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 41 G2: 41 Endpoint score, mean (SD) At week 1 G1: 55 G2: 55 At week 2 G1: 70 G2: 65 Change, mean (SD) At week 1 G1: +14 G2: +14 At week 2 G1: +29 G2: +24 • Median scores are reported; none of *P* values were significant

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Number of sessions (range, mean, SD): 3 times/wk for 2wks rTMS: • Frequency (Hz):20 • Motor threshold (%):100 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval:20 • Pulses per session: 1200 • Total number of sessions: 4/wk with 1 UL ECT *Strategy* Mixed		*Responders, n* Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 9.3 G2: 8.3	At week 1 G1: 17 G2: 20 At week 2 G1: 12 G2: 11 Change, mean (SD) At week 1 G1: -23 G2: -20 *P* = 0.1 At week 2 G1: -28 G2: -29 *P* = 0.5 Responders, n G1: 6 (54.5%) G2: 6 (54.5%) Endpoint score, mean (SD) At week 1 G1: 6.2, G2: 6.4 At week 2 G1: 3.0 G2: 5.0 Change, mean (SD) At week 1 G1: -3.1G2: -1.9 At week 2 G1: -6.3 G2: -3.3	• Comparison of gains made by ECT vs. ECT + rTMS: Awk 1 = *P* = 0.6, CI -13 - 12, Awk2 = *P* =0.2, CI -4 - 17, Awk1 +Awk2 = *P* = 0.4, CI = --8 - 17 • Median scores are reported; none of *P* values were significant • Comparison of gains made by ECT vs. ECT + rTMS: Awk 1 = *P* = 0.6, CI -13 - 12, Awk2 = *P* =0.2, CI -4 - 17, Awk1 +Awk2 = *P* = 0.4, CI = --8 - 17. *Adverse Events* Overall, % Positive responses G1: 56 G2: 31 Amnesia, % Memory Problems At Week 1 G1: 8 r, G2: 3G1:: 9 G2: 4 Headache, responses At Week 1 G1: 8 G2: 5

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At Week 2 G1: 9 G2: 6 • None of observed differences in proportions of patients having side effects were statistically significant, as judged by Fisher's exact test • It should be noted that due to small sample sizes, chance of detecting massive differences was small • At both assessments (week 1 and week 2), "memory problems" were more than twice as common inECT only stream compared to ECT + rTMS • Due to small sample sizes, statistical tests cannot exclude possiblity that difference is due to chance. muscle pains • ECT group, wk 1 = 7 responses, wk 2 = 6 responses; ECT + rTMS,wk 1 = 4, wk 2 = 4. *Attrition* NR

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adherence/ compliance NR
Author, Year Rosa et al., 2006[2] *Country, setting* Brazil, university clinic, inpatients and outpatients included *Funding* Not reported *Research Objective* To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Included completers analysis & ITT (LOCF), ITT is reported in abstraction *N* 42 *Duration* Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk Interventions G1: ECT G2: rTMS *Medications allowed* ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed *Strategy* Switch	*TRD definition* • A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Age 18-65 • unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms *Exclusion criteria* • History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease • Use of cardiac pacemaker • Pregnancy	*Treatment Failure* Previous treatment, not specified, % Overall:100% *Polarity, %* Unipolar Overal: 100% Age, mean yrs G1: 46.0 G2: 41.8 Sex, % females G1: 46.7 G2: 60.0 Race, % white G1: 80.0 G2: 90.0 *HAM-D 17* Baseline n G1: 20 G2: 22 Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20] *CGI* Baseline n G1: 20 (N analyzed =15) G2: 22 (N analyzed =20)	*HAM-D 17* Endpoint score, mean (SD) NR (graph only) Change, mean (SD) NR (graph only) *P* = 0.86 Responders, n (%) G1: 6 (20) G2: 10 (45) *P* = 0.35 Remitters, n (%) Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) *P* = 0.65 Instrument CGI Endpoint score, mean (SD) 2wk G1: 4.0 (1.0) G2: 3.7 (1.1) 4wk G1: 3.2 (1.5) G2: 3.1 (1.3) Change, mean (SD) NR, *P* = 0.672	*Quality of Life* NR *Adverse Events* Overall, % NR Suicidality, % G1: 10.0 G2: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study *Neuropsychological or executive functioning* • NS differences between groups on all neuropsychological tests following wk2 & wk4. (Weschler Adult Intelligence Scale - R subtests (Vocabulary, Cube), • Wechsler Memory Scale subtest (Digit Span), • Rivermead Behavioral Memory Test) *MMSE* NR

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS: • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks ECT: • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5)		Baseline score, mean (SD) G1: 4.7 (0.8) G2: 4.3 (0.8)		*Other* *Attrition* Overall, % 16.7 At end of treatment, % G1: 15.0* G2: 9.1* *Prior to completing txt (txt end date differed by pt) At end of follow-up, % G1: 25.0 G2: 9.1 Withdrawals due to efficacy, % G1: NR G2: 0.0 Withdrawals due to adverse events, % G1: NR G2: 9.1 Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy *Adherence/ compliance* NR

Evidence Table 2. KQ1 head to head: Tier 2

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Grunhaus et al., 2003[3] *Country, setting* Israel, single center, inpatients and outpatients *Funding* National Association for Research in Schizophrenia and Affective Disorders & Stanley Foundation *Research Objective* To compare antidepressant efficacy of rTMS and ECT in nonpsychotic major depression *Quality Rating* Fair	*Study design* RCT *Type of analysis* cannot tell, all reported patients included in analysis *N* 40 *Duration* Primary outcome after 4 weeks of txt *Medications Allowed* Patients in both groups required to taper psychotropic medications. Only lorazepram allowed regularly, benzodiazepine allowed only for sleep induction Strategy Switch Interventions G1: ECT G2: rTMS *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold	*TRD definition* All pts referred for ECT following a failure of 1+ AD (at adequate levels and for at least 4 weeks of txt) *Tier 2* *Inclusion criteria* • Age 18+ • Unipolar major depresssion (DSM IV) • HAM-D >= 18 *Exclusion criteria* • Any exclusion criteria for safety of rTMS • major depression was secondary to a general medical condition or substance abuse • pts with additional Axis I diagnoses	*Treatment Failure* Failed 2 or more, % G1: 60 G2: 65 *Polarity, %* 100% MDD Age, mean yrs G1: 61,4 G2: 57.6 Sex, % females G1: 75 G2: 70 *HAM-D 17* Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 25.5 (5.9) G2: 24.4 (3.9)	*HAM-D 17* Endpoint score, mean (SD): At week 2 G1: 15.9 (6.6) G2: 14.7 (8.8) At week 4 G1: 13.2 (6.6) G2: 13.3 (9.2) Change, mean (SD) At week 2 G1: -9.6 G2: -9.7 At week 4 G1: -12.3 G2: -11.1 Responders, n Response defined as a decrease ≥ 50% or HAM-D17 score ≤ 10 and a GAF rating ≥ 60 G1: 12 (60%) G2: 11 (55%) *P* = NS Remitters, n HAM-D17 ≤ 8 G1: 6 (30%) G2: 6 (30%) *P* = NS	*Quality of Life* Scale GAF Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 39.8 (9.3) G2: 48.9 (10.8) Endpoint score, mean (SD) At week 2 G1: 55 (12.4) G2: 58.3 (17.1) At week 4 G1: 60.6 (13.5) G2: 62.5 (18.8) Change, mean (SD) b-week 2 G1: -15.2 G2: -9.4 b-week 4 G1: -20.8 G2: -13.6 Scale Pittsburgh Sleep Quality Index Baseline n G1: 20 G2: 20

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	(%):90 • Number of trains: 20 • Length of train (seconds): 6 • Inter-train interval:60 • Pulses per session:1200 • Total number of sessions: 5/ wk over 4 wks ECT: • % receiving bilateral: 35 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 10.25 (3.1)				Baseline score, mean (SD) G1: 12.2 (4.5) G2: 10.4 (4.6) Endpoint score, mean (SD) At week 2 G1: 8.3 (3.9) G2: 9.9 (5.1) At week 4 G1: 8.6 (4.9) G2: 9.4 (5.0) Change, mean (SD) b- week 2 G1: 3.9 G2: 0.5 B week 4 G1: 3.6 G2: 1.0 *Adverse Events* Overall, % G1: NR "the ECT group was handled clinically and no special recording of side effects was done G2: NR Headache, % G1: NR G2: 15.0 Sleep disturbance: G1: NR G2:10%

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Neuropsychological or executive functioning Measures, Results Predefined MMSE Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 25.8 (3.4) G2: 27.8 (3.0) Endpoint score, mean (SD) At week 2 G1: 26.3 (2.9) G2: 28.0(2.1) At week 4 G1: 27.1(2.5) G2: 28.0 (1.8) Change, mean (SD) b-week 2 G1: -0.5 G2: -0.2 b-week 4 G1: -1.3 G2: -0.2 *Attrition* NR *Adherence/ compliance* NR

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Kocsis, 2009[4] Kocsis *Country, setting* United States Multicenter- REVAMP Study *Funding* NIMH *Research Objective* To determine the role of adjunctive psychotherapy in the treatment of chronically depressed patients with less than complete response to an initial medication trial *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers or per protocol (PP) *N* 491 *Duration* Phase I (Medication Algorithm)Only: 12 wks Phase II (Randomization Phase Meds & psychotherapy): 12 wks Primary outcome measure: HAMD and CGI Remission performed biweekly *Interventions* Antidepressant Only Antidepressant + Brief Supportive Psychotherapy Antidepressant + Cognitive behavioral analysis System of Psychotherapy G1: MEDS Only G2: MEDS + Psychotherapy G3: MEDS + Brief Supportive Psychotherapy G4: MEDS + Cognitive Behavioral Analysis	*TRD definition* • For entry into the randomization phase of study pts had to participate in open-label phase of antidepressant algorithm and had to achieve less than remission (remission defined as ≥ 60% reduction in HAMD score, HAMD total score < 8, and no longer meeting DSM-IV criteria for MDD). • Required failure in current episode *Tier 2* *Inclusion criteria* • MDE ≥ 4 wks and depressive symptoms for more than 2 yrs without remission; Diagnosis of double depression, chronic major depression, recurrent depression with incomplete recovery between episodes; 18-75 yo; HAM-D24 score ≥ 20; English speaking; informed consent; understanding of the nature of the study	*Subgroups* Chronic Depression *Baseline n* G1: 96 G2: 395 G3: 195 G4: 200 *Treatment Failure* Failed 1 or more, % G1: 100 G2: 100 G3: 100 G4: 100 *Polarity, %* Unipolar G1: 100 G2: 100 G3: 100 G4: 100 *Patient Characteristics* *Age, mean yrs* G1: 43.2 G2: 45.9 G3: 46.4 G4: 45.3 G1: vs. G2: p = 0.05 *Sex, % females* G1: 49.0 G2: 57.0 G3: 57.9 G4: 56.0	*HAM-D (Insert #)* Yes HAMD24 G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP *N analyzed* Baseline G1: 94 G2: 384 G3: 189 G4: 195 Week 2: G1: 92 G2: 370 G3: 181 G4: 189 Week 4: G1: 85 G2: 359 G3: 176 G4: 183 Week 6: G1: 80 G2: 346 G3: 170 G4: 176 Week 8: G1: 84 G2: 341 G3: 168 G4: 173 Week 10: G1: 79 G2: 333	*Quality of Life* Yes Scale Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) Intervention G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP Baseline n Baseline G1: 77 G2: 306 G3: 154 G4: 152 Week 4: G1: 81 G2: 342 G3: 171 G4: 171 Week 8: G1: 80 G2: 326 G3: 162 G4: 164 Week 12: G1: 75 G2: 334 G3: 162 G4: 172

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	System of Psychotherapy (CBASP) G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP *Medications Allowed* Next step medication in the following sequence: Sertraline; escitalopram, ibuprorpion, venlafaxine, mirtazapine, and/or lithium augmentation During first 4 weeks, if intolerant moved to next level of sequence *Strategy* Combination *Parameters* G1: Meds only G2: Meds + plus either CBASP or BSP G3: Meds + BSP: includes, reflective listening, empathy, evoking affect, therapeutic optimism, and acknowledgment of	*Exclusion criteria* • Pregnancy; current diagnosis of any psychotic disorder, history of bipolar disorder; dementia; principal diagnosis of PTSD, AN, BN, OCD; antisocial, schizotypal or severe borderline personality disorder; current alcohol or other substance-related dependence requiring detoxification (exception nicotine dependence); previous treatment with cognitive behavioral analysis system of psychotherapy (CBASP) failing at least 4 of the treatment steps in pharmacotherapy algorithm; unwilling to terminate other forms of psychiatric treatment; serious unstable or terminal medical illness	*Race, % white* G1: 85.4 G2: 89.6 G3: 89.2 G4: 90.0 G1: vs. G2, p = 0.03 *Not Specified, %* G1: NR G2: NR G3: NR G4: NR *Right handed, %* G1: NR G2: NR G3: NR G4: NR *Groups similar at baseline* There were small but statistically significant differences in Race (p = 0.03) and Age (p = 0.05) in the MEDS only vs. MEDS +Psychotherapy comparison. *HAM-D 17* Baseline score, mean (SD) G1: 18.37 (8.00) G2: 19.48 (8.27) G3: 19.44 (8.31) G4: 19.52 (8.26)	G3: 163 G4: 170 Week 12: G1: 76 G2: 342 G3: 168 G4: 174 Endpoint score, mean (SD) Week 2: G1: 16.82 (9.21) G2: 17.87 (8.55) G3: 18.14 (8.99) G4: 17.61 (8.13) Week 4: G1: 15.27 (9.46) G2: 17.09 (8.49) G3: 17.24 (8.04) G4: 16.94 (8.92) Week 6: G1: 13.74 (7.97) G2: 15.55 (8.65) G3: 16.28 (8.70) G4: 14.85 (8.57) Week 8: G1: 13.71 (8.54) G2: 14.74 (8.45) G3: 15.08 (8.26) G4: 14.42 (8.65) Week 10: G1: 13.66 (8.52) G2: 14.04 (8.90) G3: 14.94 (9.38) G4: 13.18 (8.36) Week 12: G1: 12.28 (8.44) G2: 12.02 (8.39)	Baseline score, mean (SD) G1: 12.64 (3.01) G2: 12.70 (3.05) G3: 12.71 (3.14) G4: 12.69 (2.96) Endpoint score, mean (SD) Week 4: G1: 12.07 (3.54) G2: 11.96 (3.15) G3: 12.13 (3.15) G4: 11.78 (3.14) Week 8: G1: 11.15 (3.33) G2: 11.50 (3.29) G3: 11.76 (3.28) G4: 11.25 (3.30) Week 12: G1: 10.96 (3.63) G2: 10.48 (3.36) G3: 10.73 (3.46) G4: 10.24 (3.25) Change, mean (SD) At wk 12, Calculated: G1: -1.68 G2: -2.22 G3: -1.98 G4: -2.45 Other Mixed-effects linear regression: G1: vs. G2, p = 0.31 G3 vs. G4, p = 0.09

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	patients' assets; specific interpresonal, cognitive, behavioral, and psychodynamic interventions were strictly proscribed; Administered for 16 -20 sessions during 12 wks of treatment. G4: Meds + CBASP: structured CBT with a structured interpersonal problem-solving algorithm; Administered twice weekly during weeks 1 - 4 and weekly through wks 5 -12; 16 total sessions.			G3: 12.77 (8.45) G4: 11.29 (8.30) Change, mean (SD) At 12 weeks, calculated: G1: -6.09 (NR) G2: -7.46 (NR) G3: -6.67 (NR) G4: -8.23 (NR) Responders, n Partial Response Week 2 G1: 6 G2: 33 Week 4 G1: 9 G2: 31 Week 6 G1: 8 G2: 48 Week 8 G1: 9 G2: 51 Week 10 G1: 8 G2: 53 Week 12 G1: 16 G2: 89 Full Response Week 2 G1: 7 G2: 9 Week 4 G1: 10 G2: 22 Week 6 G1: 13	Interaction between treatment and time: G1: vs. G2, p = 0.27 G3 vs. G4, p = 0.52 Scale Intervention Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % NR Dizziness, % NR

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: 31 Week 8 G1: 13 G2: 47 Week 10 G1: 13 G2: 57 Week 12 G1: 11 G2: 52 Remitters, n Week 2 G1: 17 G2: 46 G3: 26 G4: 20 Week 4 G1: 24 G2: 50 G3: 21 G4: 29 Week 6 G1: 23 G2: 71 G3: 30 G4: 41 Week 8 G1: 23 G2: 76 G3: 33 G4: 43 Week 10 G1: 21 G2: 89 G3: 39 G4: 50 Week 12	Headache, % NR Insomnia, % NR Post op complications, % NR Somnolence, % NR Suicidality, % NR Additional Comments NA Utilized the Frequencey, Intensity and Burden of Side Effects Rating form: Moderate Intensity (% of patients): G1: 17.7 G2: NR G3: 27.0 G4: 26.2 Moderate burden (% of patients): G1: 8.3 G2: NR G3: 11.8 G4: 14.0 *Neuropsychological or executive functioning* No

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G1: 30 G2: 119 G3: 52 G4: 67 Other Response: Categorical status as remitter, nonresponder or partial responder. Remitter: HAM-D score of < 8 that had decreased by at ≥ 50% from baseline and having a CGI score of 1 or 2 for 2 consecutive visits. Partial responder: havina Ham-d score of 8-16 that had decreased by at ≥ 50% from baseline and having a CGI score of ≤ 3 or HAM-D score of < 8 and CGI of 1 or 2 for 1 wk but not 2 consecutive wks Nonresponder: not meeting criteria of remitter or a partial responder. Mixed-effects linear regression analysis: G1: vs. G2, p = 0.67 G3 vs. G4, p = 0.04 Mixed-effects ordinal logistic regression analyses:	Measures, Results NR Predefined Yes MMSE No Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other *Other* Yes Utilized the Frequencey, Intensity and Burden of Side Effects Rating form: Moderate Intensity (% of patients): G1: 17.7 G2: NR G3: 27.0 G4: 26.2 Moderate burden (% of patients): G1: 8.3 G2: NR G3: 11.8

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G1: vs. G2, p = 0.39 G3 vs. G4, p = 0.06 Treatment x time interaction: G1: vs. G2:, p = 0.03 G3 vs. G4, p = 0.79 HAMD Remission (<8) G1: 30 (31.3) G3: 52 (26.7) G4: 67 (33.5) P = NR *QIDS* Intervention G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP *N analyzed* G1: 89 G2: 365 G3: 179 G4: 186 Week 2: G1: 88 G2: 347 G3: 170 G4: 177 Week 4: G1: 81 G2: 351 G3: 171 G4: 180 Week 6: G1: 75 G2: 336	G4: 14.0 Adequate information Yes *Attrition* Overall, % 13.8 At end of treatment, % G1: 16.6 G2: 13.2 G3: 13.8 G4: 12.5 At end of followup, % G1: NA G2: NA G3: NA G4: NA Withdrawals due to efficacy, % G1: 5 (5.2%) G2: 5 (1.3%) G3: 4 (2.1%) G4: 1 (0.5%) Withdrawals due to adverse events, % G1: 2 (2.1%) G2: 3 (0.8%) G3: 1 (0.5%) G4: 2 (1.0%)

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G3: 166 G4: 170 Week 8: G1: 82 G2: 326 G3: 161 G4: 165 Week 10: G1: 77 G2: 323 G3: 154 G4: 169 Week 12: G1: 73 G2: 330 G3: 162 G4: 168 Baseline score, mean (SD) G1: 10.16 (4.50) G2: 10.85 (4.77) G3: 10.89 (4.79) G4: 10.82 (4.76) Endpoint score, mean (SD) Week 2: G1: 9.10 (5.19) G2: 9.90 (4.64) G3: 10.20 (4.88) G4: 9.60 (4.39) Week 4: G1: 8.49 (5.51) G2: 9.27 (4.65) G3: 9.50 (4.65) G4: 9.04 (4.66)	Other NOTE: Study compares G1: vs. G2 and G3 vs. G4; G3 and G4 make up G2. *Adherence/ compliance* Adherence Number of Sessions attended: mean (SD, Range) G3: 13.2 (7.0, 0 - 21) G4: 12.6 (6.7, 0 - 19) Association of # of sessions attende and probability of remission: G3: 1.01, p = 0.62) G4: 1.02, p = 0.43)

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 6: G1: 7.69 (4.56) G2: 8.81 (4.76) G3: 9.25 (4.97) G4: 8.38 (4.52) Week 8: G1: 7.95 (5.12) G2: 8.27 (4.60) G3: 8.47 (4.59) G4: 8.08 (4.60) Week 10: G1: 7.60 (4.61) G2: 7.62 (4.83) G3: 8.03 (4.89) G4: 7.25 (4.77) Week 12: G1: 7.49 (5.24) G2: 6.96 (4.59) G3: 7.30 (4.41) G4: 6.63 (4.76) Change, mean (SD) Calculated: G1: -2.67 (NR) G2: -3.89 (NR) G3: -3.58 (NR) G4: -4.19 (NR) Other Remission defined as having a total score of 6. Significance NR Remission, #: Week 2 G1: 24 G2: 64 G3: 32 G4: 32	

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 4 G1: 29 G2: 94 G3: 45 G4: 49 Week 6 G1: 27 G2: 93 G3: 43 G4: 50 Week 8 G1: 28 G2: 101 G3: 47 G4: 54 Week 10 G1: 32 G2: 126 G3: 56 G4: 70 Week 12 G1: 32 G2: 152 G3: 67 G4: 85	

Evidence Table 3. KQ1 head to head: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Chistyakov et al., 2005[5] *Country, setting* Israel, single psychiatry department, inpatients *Funding* Not reported *Research Objective* To investigate changes in cortical excitability following ECT in patients with major depression (MD) and to compare therapeutic efficacy of ECT combined with rTMS to that of ECT alone. *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell type of analysis – all reported patients included *N* 22 *Duration* Primary outcome at 3 weeks Interventions G1: ECT+ rTMS G2: ECT + placebo *Medications Allowed* All antidepressants were tapered and discontinued 1 week before start and no patients received anticonvulsant mood stabilizers *Strategy* Switch *Parameters* ECT: • % receiving bilateral: 100 • Intensity: NR	*TRD definition* Patients referred for ECT, AD failures were not required. *Tier 3* *Inclusion criteria* • DSM IV criteria for major depression • age was between 20 and 75 years *Exclusion criteria* • Suicidal risk • any central or peripheral nervous system disease, • seizure disorder, • history of head trauma in last year, • systemic uncontrolled disease, • pacemaker or metallic implants • drug or alcohol abuse	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD Age, mean yrs G1: 59.2 G2: 54.0 Sex, % females G1: NR G2: NR Overall: 68 HAM-D Baseline n G1: 12 G2: 10 Baseline score, mean (SD) Reported in graph only	*HAM-D* Endpoint score, mean (SD)NR Change, mean (SD) NR Group x time, $P > 0.05$ Responders, n G1: NR G2: NR Overall: 19 (86%) P = NR (ns)	*Quality of Life* NR *Adverse Events* NR *Neuropsychological or executive functioning* No Measures, Results NR Predefined No MMSE NR *Attrition* NR *Adherence/ compliance* NR

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Number of sessions (range, mean, SD): 2/wk rTMS • Frequency (Hz):1 • Motor threshold (%):110 • Number of trains: NR • Length of train (seconds): NR • Inter-train interval: NR • Pulses per session: 900 • Total number of sessions: 4/wk for 3 weeks Sham rTMS • Coil was held perpendicularly to scalp surface. • Patients received 4 sessions/wk				
Author, Year Hansen, 2010[6] Hansen *Country, setting* Denmark University Hospital Inpatient Psychiatric *Funding* Danish Council for Medical Research; Einar Geert-Jorgensen and Wife Ellen Geert-Jorgensen Research Foundation; Boutcher Worzner and wife Inger	*Study design* RCT *Type of analysis* ITT PP *N* 60 *Duration* Active treatment: 3 wks HAMD and UKU assessed at baseline and weekly intervals w/in 24 hrs of treatment	*TRD definition* • Patients referred for ECT *Tier 3* *Inclusion criteria* • 18-80 yo; HAMD-17 total score of ≥ 20 and/or subscale score of ≥ 9; right-handed; ICD-10 diagnosis of moderate to severe depression; DSM-IV diagnosis of MDD; unipolar or bipolar	*Subgroups* No Subgroups *Baseline n* G1: 30 G2: 30 *Treatment Failure* Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR	*HAM-D (Insert #)* Yes HAM-D17 G1: rTMS G2: ECT Endpoint score, mean (SD) Week 3 G1: NR Baseline - wk3 reduction, p <0.001 G2: NR	*Quality of Life* No *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Worzner grant; the Aarhus University Foundation for Researhc in Mental Disease; the Foundation of Psychiatric Research Research Objective To compare the antidepressant efficacy and adverse effects of right prefrontal low-frequency rTMS with that of ECT. *Quality Rating* Fair - KQ1 KQ4?	Follow-up treatment: 7 wks (total duration) HAMD and UKU assessed at wk 5 and wk 7 *Interventions* ECT rTMS G1: rTMS G2: ECT *Medications Allowed* Continued current antidepressant medication; discontinued antiepileptics prescribed as mood stabilizers, benzodiazepines tapered off, low dose zopiclone or zopidem if needed for sleep *Strategy* Augment or add-on strategy *Parameters* G1: Location: Right DLPFC Frequency: 1 Hz Intensity: 110% MT Trains: 2 60s trains Intertrain interval: 180 s Number of session: 15 total (1 per week day for	*Exclusion criteria* • Organic brain damage; personal/family history of epileptic seizures, metallic objects in the chest or brain as a result of surgery; cardia pacemakers; somatic diseases associated w/ brain dysfunction; pregnancy; use of coercive measures; suicidal risk of severe degree; severe agitation; delirium; alcohol or drug dependence.	Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar G1: 86.7 G2: 86.7 Bipolar I G1: 13.3 G2: 13.3 Bipolar II G1: NR G2: NR *Patient Characteristics* *Age, mean yrs* Median (range) G1: 46 (14-38) G2: 52 (29-79) p = 0.16 *Sex, % females* G1: 76.7 G2: 63.3 *Race, % white* G1: NR G2: NR	Baseline - wk3 reduction, p <0.001 Week 3-7 G1: NR wk3 - wk7 reduction, p <0.001 G2: NR wk3 - wk7 reduction, p = 0.78 Week 7 G1: NR Baseline - wk 7 reduction, p < 0.001 G2: NR Baseline - wk 7 reduction, p < 0.001 Change, mean (SD) G1: NR G2: NR Responders, n Response Rate Difference Week 3, Rate (95% CI): G1: 0.20 (0.08-0.39) G2: 0.57 (0.37-0.75) G1: vs. G2 rate difference: 0.37 (0.14-0.59), p = 0.003 Week 7, Rate (95%CI): G1: 0.43 (0.25-0.63) G2: 0.60 (0.41-0.77) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200	Cognitive impairment, % G1: 0 G2: 0 Dizziness, % NR Headache, % NR Insomnia, % NR Post op complications, % NR Somnolence, % Signficantly > decline in fatigue score in the ECT group (score NR) Suicidality, % NR Additional Comments NR "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience.

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	3 weeks) G2: Location: Unilaterally over the right hemisphere Intensity: Recorded seizure duration ≥ 25 seconds; If between 15-25 seconds next treatment carried out with 50% higher stimulus intensity; If < 15 seconds then followed by restimulation. Number of session: 9 total (3 sessions weekly)		*Not Specified, %* G1: NR G2: NR *Right handed, %* G1: 100 G2: 100 Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) Median (Range): G1: 24 (14-38) G2: 24 (16-34) G1: vs. G2: p = 0.68	Remitters, n Remission Rate Difference Week 3 Rate (95% CI): G1: 0.27 (0.12 - 0.46) G2: 0.53 (0.34 - 0.72) G1: vs. G2 rate difference: 0.26 (0.03 - 0.51), p = 0.035 Week 7 Rate (95% CI): G1: 0.40 (0.23 - 0.59) G2: 0.57 (0.37 - 0.75) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200 Other Remission: HAMD-17 ≤ 12 Response: ≥ 50% reduction in HAMD-17	Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale. *Neuropsychological or executive functioning* Yes Measures, Results Logical Memory – Immediate recall Baseline, Mean (SD): G1: 10.8 (4.4) G2: 10.0 (5.1) After Treatment G1: 8.8 (3.8) G2: 9.6 (5.1) Logical Memory – Delayed recall Baseline, Mean (SD): G1: 7.6 (5.4) G2: 7.46 (5.5) After Treatment G1: 7.2 (3.7) G2: 6.8 (5.8) Verbal Learning – Total Baseline, Mean (SD) G1: 8.2 (1.7)

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G2: 8.4 (2.1) After Treatment G1: 8.1 (2.0) G2: 7.9 (1.5) Verbal Learning – delayed recall Baseline, Mean (SD) G1: 5.9 (2.3) G2: 5.5 (2.0) After Treatment G1: 6.0 (2.6) G2: 4.8 (3.1) Rey Complex Figure – copy Baseline, Mean (SD) G1: 32.9 (4.2) G2: 29.7 (7.4) After Treatment G1: 33.6 (2.2) G2: 29.2 (6.8) Rey Complex Figure – delayed recall Baseline, Mean (SD) G1: 16.0 (6.2) G2: 13.9 (7.2) After Treatment G1: 25.6 (7.4) G2: 13.1 (9.4) G1: vs. G2, p <0.01 Within groups, p <0.01 Trail-Making Test A Baseline, Mean (SD) G1: 65.7 (35.5) G2: 64.7 (23.5) After Treatment G1: 60.6 (39.4) G2: 65.9 (34.0) Trail-Making Test B

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Baseline, Mean (SD) G1: 147.8 (64.4) G2: 131.3 (50.1) After Treatment G1: 131.0 (68.0) G2: 107.8 (36.0) SDMT Baseline, Mean (SD) G1: 29.9 (12.0) G2: 29.3 (13.7) After Treatment G1: 34.0 (12.6) G2: 31.1 (14.0) Verbal Fluency – letter S Baseline, Mean (S) G1: 10.4 (3.8) G2: 11.6 (7.3) After Treatment G1: 12.9 (5.6) G2: 10.3 (6.1) Verbal Fluency – animals Baseline, Mean (SD) G1: 18.4 (6.3) G2: 16.3 (4.5) After Treatment G1: 19.8 (6.2) G2: 14.11 (3.1) G1: vs. G2, $p < 0.05$ Other Yes "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients,

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale. Adequate information Yes *Attrition* Overall, % 30 At end of treatment, % G1: 33.3 G2: 26.7 At end of followup, % G1: NR G2: NR

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to efficacy, % G1: NR G2: NR Withdrawals due to adverse events, % G1: NR G2: NR Other Withdrawal due to Discomfort at the stimulus site, % (n): G1: 16.7 (5) G2: 0 (0) Withdrawal due to serious deterioration, % (n): G1: 10 (3) G2: 3 (1) Withdrawal due to somatic disease, % (n): G1: 3 (1) G2: 0 (0) Withdrawal due to Commotio cerebri, % (n): G1: 0 (0) G2: 3 (1) Withdrawal for unknown reasons, % (n): G1: 0 (0) G2: 3 (1) *Adherence/ compliance* None reported

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year McLoughlin et al., 2007[7] Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); byGuy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating major depressive episodes in patients referred for ECT	*Study design* RCT- pragmatic and single blinded (raters) *Type of analysis* m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months Interventions G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan) *Strategy* Augmentation	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % Age, mean yrs G1: 63.6 G2: 68.3 Sex, % females G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0) *BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93 Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This suggests that treatment by rTMS does not provide any additional

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Quality Rating Good	*Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5			Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25 Responders, n NR Remitters, n NR	gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR *Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU 6 mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory)

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					MMSE Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects. *Attrition* Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, %

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 4. KQ1 active versus control: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] *Country, setting* USA, Single center, University department of psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint *Interventions* G1: High-left TMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years	*Subgroups* Pain, subgroup analysis presented in Avery et al, 200711 *Baseline n* G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 44.3 G2: 44.2 *Sex, % females* G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR	*HAM-D 17* Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time *P* = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) *P* = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) *P* = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) *BDI* Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, *P* < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR) *Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT,

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• history of substance abuse or dependence withinpast 2 years, • antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity	Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)	significant group by time interaction (P = 0.003)	and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% (P < 0.05) no statistically significant (P > 0.05) time by treatment group interactions for any of neuropsychological test measures. models were refit without interaction term, there was no significant treatment group main effect (P > 0.05) evident for any of neuropsychological tests, indicating groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant (P > 0.05) differences between groups for any session.

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					MMSE NR *Attrition* Overall, % 7.4% (5/68) At end of treatment, % NR At end of followup, % NR Withdrawals due to efficacy, % G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued *Adherence/ compliance* NR
Author, Year Bocchio-Chiavetto et al., 2008[12] *Country, setting* Italy, Conducted at a single psychiatric unit, patient status NR	*Study design* RCT, crossover *Type of analysis* All reported patients included in the analysis *N* 36	*TRD definition* • 2+ failures (8+ weeks at standard doses) from 2+ classes of antidepressants • Required to be in current episode	*Subgroups* Genotypes: 5-HTTLPR (LL or S carriers) BDNF Val66Met (Val/Val or Met carriers) Baseline N	*HAM-D 21* Endpoint score, mean (SD) G1: 17.5 (6.91) G2: 21.13 (4.53) 5-HTTLPR G3: 40.49 (25.27) G4: 8.78 (4.23)	*Quality of Life* NR *Adverse Events* NR *Neuropsychological or executive functioning* No

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Funding Ministero dlla Sanita RC 2000 *Research Objective* To evaluate if rTMS is an effective treatment for TRD *Quality Rating* Fair	*Duration* 5 days of txt (8 week between crossover) Primary endpoint following 1 week of treatment Interventions G1: Overall active G2: Overall sham *5-HTTLPR genotypes* G3: LL Active G4: LL Sham G5: S Active G6: S Sham *BDNF Val66Met* G7: Val/Val Active G8: Val/Val Sham G9: Met Active G10: Met Sham *Medications Allowed:* • Patients allowed to continue on typical and atypical psychotics • 24 patients on mono- or combined therapies with SSRIs • 12 on other antidepressants (7 on typical, 5 on atypical antipsychotics) • Mean dose as imipramine equivalents = 148.56 ±49.77	*Tier 1* *Inclusion criteria* • HAM-D 21 ≥ 17 • TRD *Exclusion criteria* • Pregnancy, major medical, or neurological disorder	G1: 36 G2: 15 G3: 10 G4: 3 G5: 26 G6: 12 G7: 20 G8: 10 G9: 16 G10: 5 Treatment Failure Mean failed trials G1: NR G2: NR G3: 2.80 (0.79) G4: NR G5: 2.92 (1.21) G6: NR G7: 2.79 (0.98) G8: NR G9: 3.00 (1.25) G10: NR Overall: 2.89 *Polarity, %* MDD G1: 86.1% Bipolar G1: 13.9% Age, mean yrs G1: 59.67 Sex, % females G1: 80.5 Race, % white G1: 100%	G5: 19.44 (17.51) G6: 14.11 (16.86) G3 vs G5, *P* = 0.008 G4 vs G6, *P* = 0.605 BDNF G7: 32.36 (21.33) G8: 16.52 (10.64) G9: 16.45 (19.90) G10: 6.11 (12.46) G7 vs G9, *P* = 0.028 G8 vs G10, *P* = 0.233 Change, mean (SD) G1: -5.69 G2: -3.40 *P* = NR % Change G1: 25.29% (NR) G2: 13.05% (NR) *P* = NR	MMSE No *Attrition* NR *Adherence/ compliance* NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Augmentation *Parameters* rTMS Low • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 40 • Length of train (seconds):10 • Inter-train interval: 20 • Pulses per session: 400 • Total number of sessions: 5 in 5 days High • Frequency (Hz):17 • Motor threshold (%):110 • Number of trains: 8 • Length of train (seconds): 3 • Inter-train interval: 120 • Pulses per session: 408 • Total number of sessions: 5 in 5 days Sham: • 25mm thick plywood shield, built to appear as an integral part of apparatus, was		*HAM-D 21* Baseline score, mean (SD) G1: 23.19 (5.12) G2: 24.53 (4.79) G3: 23.40 (6.64) G4: NR G5: 23.12 (4.56) G6: NR G7: 24.10 (5.60) G8: NR G9: 22.06 (4.34) G10: NR		

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	interposed between the coil itself and scalp, separating the two ones. Ventral surface of coil upside down and stimulus intensity substantially decreased at 60% below motor threshold				
Author, Year Boutros et al., 2002[13] *Country, setting* US, Yale School of Medicine and VA-Connecticut, outpatient *Funding* VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer *Research Objective* To provide additional data on effiacy and safety for rTMS as an augment strategy in TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 21 *Duration* 2 weeks txt; follow up with responders for up to 20 weeks post txt *Interventions* G1: rTMS G2: Sham *Medications Allowed* Pts allowed to continue all current psychotropic meds *Strategy* Augmentation, 3 pts in active and 1 in sham	*TRD definition* • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major Depression • HAM-D25 >= 20 *Exclusion criteria* • Suicidality • "Prominent" psychotic sympotms • History of neurological disorders • current drug abuse	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 100% *Age, mean yrs* G1: 49.5 G2: 52.0 *Sex, % females* G1: 25 G2: 10 *Right handed, %* G1: 90.9 G2: 88.9 *HAM-D* Baseline n G1: 12 G2: 9	*HAM-D* Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 *P* = NS Responders, n Defined as 30% improvement on HAM-D G1: 7 G2: 2 Responders, n (%) Defined as 50% improvement on HAM-D G1: 3 G2: 2 *Relapse* Of 6 active treatment responders inluded	*Quality of Life* NR *Adverse Events* Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6 Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	txt were not on any meds *Parameters* rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 58 • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp		Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)	in20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in thh 20-week follow-up, 1 relapsed.	*Attrition* Overall, % 18.2% (4/22) At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10) At end of followup, % NR Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR *Adherence/ compliance* NR
Author, Year Fitzgerald et al., 2006[14] *Country, setting* Australia, single center *Funding* Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for	*Study design* RCT *Type of analysis* ITT (LOCF) *N* 50 *Duration* 2 wks double blind with those with >20% decrease in MADRS to	*TRD definition* • 2+ failed medications with txt duration ≥6 wks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • DSM-IV diagnosis of Major Depressive Episode	*Treatment Failure* Mean failed AD trials (lifetime) G1: 5.6 (3.1) G2: 6.2 (3.0) *Polarity, %* Unipolar G1: 84% G2: 84% Bipolar G1: 16% G2: 16%	*HAM-D 17* Endpoint score, mean (SD) NR Change, % decrease (SD) G1: 45.2% (40.1) G2: 5.4% (23.1) *P* < 0.001 Change, mean G1: -10.17 G2: -1.07	*Quality of Life* GAF Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9) Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [*P* <0.05] Change, mean (SD)

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald) *Research Objective* rTMS versus placebo for depression *Quality Rating* Good	continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary outcome after 2 and 6 weeks of txt Interventions G1: rTMS G2: Sham *Medications allowed* • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, • Antipsychotic medication, • Benzodiazepines *Strategy* Augmentation, 23% not taking medication at study entry *Parameters* rTMS Low Right: Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 3	• MADRS ≥ 20 *Exclusion criteria* • Significant medical illness • Neurological disorders • Other axis I psychiatric disorders	Age, mean yrs G1: 46.8 G2: 43.7 Sex, % females G1: 60 G2: 64 *HAM-D 17* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4) *BDI* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9) *MADRS* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)	Responders, n (%) At 6wks G1: 13 (52.0) G2: 2 (8.0) *P* = 0.001 Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0) *P* = NR *BDI* Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7) At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8) At 6 weeks G1: 9.2 (6.7) G2: NR Change, mean (SD) At week 2 G1: 10.9 G2: 7.7 At 4 weeks G1: 18.7 G2: 8.3 At 6 weeks G1: 20.0 G2: NR, *P* = 0.01	G1: 10.2 G2: 1.1 GAF Scale (t=2.0, df=40.2, *P* < 0.05) *Adverse Events* Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved ondigit span backward test improved in rTMS only (group by time: *P* = 0.07). Controlled Oral Word Association test improved for both groups (time: *P* = 0.001). Nausea 12% vs. 0, No seizures or manic episodes; *Neuropsychological or executive functioning* Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction Digit span backward Test

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 Sequential High Left: • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 • Total number of sessions: 10 sessions/day, 5 days/wk Sham: • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides)			Responders, n NR Remitters, n NR *MADRS* Endpoint score, mean (SD) At week 2 G1: 26.2 (10.2) G2: 30.9 (8.2) At week 4 G1: 11.7 (7.1 G2: 34.5 (12.0) At week 6 G1: 8.9 (7.9) G2: NA Change, mean (SD) At week 2 G1: 7.8 G2: 3.2 At week 4 G1: 22.3 G2: 0.4 (increased) At week 6 G1: 25.1 G2: NA Group by time, *P* = 0.001 at all time points	Performance improved in rTMS only (group by time: *P* = 0.07). Controlled Oral Word Association Test **I**mproved for both groups *P* = 0.001 MMSE NR *Other* Nausea 12% vs. 0 No seizures or manic episodes; *Attrition* Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78 After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn At end of treatment, % G1: 0 G2: 12 At end of follow-up, % G1: 56 G2: 100

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Responders, n At 6 weeks G1: 11 G2: 2 *P* < 0.05 Remitters, n MADRS < 10 At 6 weeks G1: 9 G2: 0 *P* = 0.005 At week 2 G1: 2 G2: 0 Follow-up at week 3 G1: 3 G2: 0 Follow-up at week 4	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR
Author, Year Fitzgerald et al., 2003[15] *Country, setting* Australia 2 general psychiatric services, outpatients *Funding* National Health and Medical Research Council and a grant fromStanley Medical	*Study design* RCT *Type of analysis* ITT *N* 60 *Tier 1*	*TRD definition* • Failed a minimum of 2 courses of antidepressant medications (6+ weeks) • Not required or not specified to be in current episode *Inclusion criteria* • DSM-IV diagnosis of Major Depression	*Treatment Failure* Mean failed trials Overall (SD) 5.68 (3.40) Polarity, % Bipolar I G1: 5 G2: 5 G3: 20 Age, mean yrs G1: 42.2 G2: 45.55 G3: 49.15	*BDI* Endpoint score, mean (SD) At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7) Change, mean (SD) At 2 weeks G1- 6.4 G2: -7.8	*Quality of Life* GAF Global Assessment of Functioning Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Institute *Research Objective* To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group *Quality Rating* Good	*Duration* Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt. Interventions G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham *Medications Allowed* 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics *Strategy* Augmentation *Parameters* rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60	(included bipolar depression) *Exclusion criteria* • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders	Sex, % females G1: 40 G2: 35 G3: 55 Right handed, % G1: 90 G2: 100 G3: 85 *BDI* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10) *MADRS* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)	G3: -2.3 *P* = 0.03 *MADRS* Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5) Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) *P* = 0.004 G1: vs. G3, G2 vs. G3, *P* < 0.005 Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) *P* = 0.07 Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5)	Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8) Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Quality of Life* Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Adverse Events* Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS.

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week			G3: 0 *P* = NR CGI Endpoint score, mean (SD) NR *P* =.01	• Although there was no difference in incidence of these adverse effects (*P* =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour. • Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: • One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium *Neuropsychological or executive functioning* • No deterioration in performance was found in any cognitive measures in group as a whole or in

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance onverbal paired associates (t50=−7.3; *P* < 0.001), verbal fluency (t48=−3.8;*P* < 0.001), and digit span forwards (t48=−1.8; *P* = 0.003) subscales;Personal Semantic Memory Schedule (t50=−2.4;*P* = 0.02); andAutobiographical Memory Schedule (t50=−1.9; *P* = 0.05). • A similar pattern of improvements was seen for each oftreatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance oncognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores acrosssame times. MMSE NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other *Attrition* Overall, % None in initial 2 week treatment phase At end of treatment, % 0 At end of follow-up, % NR But at least 28.3% did not continue on thru2nd 2 weeks Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear *Adherence/ compliance* NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Author, Year Garcia-Toro et al., 2001[16] *Country, setting* Spain, Inpatient/outpatient status not clearly reported *Funding* NOTE: CANNOT TELL IF FUNDER IS NON-PROFIT. Association for rehabilitation and social integration of mental patients (ARISPAM) & Madrid community physical handicapped Coordinator *Research Objective* To clarifyrole played byHF-rTMS applied onleft DLPC as a coadjuvant topharmocological treatment of TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 40 *Duration* Primary outcome after 2 weeks of treatment. Pts also assessed at 2 weeks follow up post txt *Interventions* G1: rTMS G2: Sham rTMS *Medications allowed* • stable treatment with antidepressants • most pts taking benzodiazepines *Strategy* Augmentation *Parameters* rTMS • Frequency (Hz): 20 • Motor threshold (%): 90 • Number of trains: 30 • Length of train (seconds): 2	*TRD definition* • 2+failed trials at maximum tolerated dose for 6+ weeks • Required to be in current episode *Tier 1* *Inclusion criteria* • 18+ years of age • Unipolar depresssion (DSM IV) *Exclusion criteria* Previous seizures or neurosurgery, current serious or uncontrolled medical illness, pacemakers, hearing aids, pregnancy or inadequate contraception for females, high suicide risk	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 51.5 G2: 50.0 *Sex, % females* G1: 41.2 G2: 44.4 *Right handed, %* 100 *HAM-D 17* Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 27.11 (6.65) G2: 25.6 (4.92) *BDI* Baseline n G1: 20; Analyzed 17 G2: 20; 18	*HAM-D 17* N analyzed G1: 17 G2: 18 Change, mean (SD) At week 1 G1: -4.52(4.66) G2: -2.87(4.27) *P* = 0.297 At week 2 G1: -7.05 (5.66) G2: -1.77(3.78) *P* = 0.003 2 week follow up G1: -8.17(7.69) G2: -2.05(6.07) *P* = 0.013 Responders, n (%) G1: 5 (25) G2: 1 (5) P=NR *BDI* Endpoint score, mean (SD) NR Change, mean (SD) At 2 weeks G1: -1.35(4.44) G2: -2.75(4.28) *P* = 0.299	*Quality of Life* NR *Adverse Events* NR Additional Comments "most frequency side effects were scalf discomfort and slight and transitory headaches in approximately a third ofcases, nearly all from stimulation group" *Neuropsychological or executive functioning* No Measures, Results NR Predefined No MMSE NR Adequate information No *Attrition* Overall, % 12.5 (5/40) At end of treatment, % NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	• Inter-train interval: 20-40 • Pulses per session: 1200 • Total number of sessions: 10 in 10 days Sham: • Edge was placed at 90 degrees		Baseline score, mean (SD) G1: 27.0 (9.05) G2: 26.38(5.60) CGI-S **CGI subscale not specified inarticle** Baseline score, mean (SD) G1: 476 G2: 4.88	2 week follow up G1: -4.05 (6.72) G2: -1.66(6.89) *P* = 0.307 *CGI-S* Change, mean (SD) At week 2 G1: -0.82(0.80) G2: -0.27(0.66) *P* = 0.04 2 week follow up G1: -1.00(1.17) G2: +0.27(0.95) *P* = 0.037	At end of follow up, % G1: 15 G2: 10 Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2: Other 3 patients in txt group w/drew because of changes in pharmacotherapy, in sham group: 1 "prefered a change in treatment" andother was abusing alcohol and thus removed fromstudy. *Adherence/ compliance* NR
Author, Year Garcia-Toro et al., 2006[17] *Country, setting* Spain, single center, all outpatients *Funding* Fundacio La Marato de TV3	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 30	*TRD definition* • Failed 2+ txt trials at 4+ weeks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • At least 18 yrs old,	*Subgroups* None *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100%	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10) At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Research Objective To assess the efficacy of high and low frequency rTMS and different locations of activation *Quality Rating* Fair	*Duration* • Primary outcome after 2 weeks of active treatment • Follow up: 2 weeks post treatment *Interventions* G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam) *Medications allowed* All pts continued (failed) AD medication and other psychotropic meds *Strategy* Augmentation *Parameters* rTMS Low: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session:	MDD, unipolar *Exclusion criteria* • Contraindications for rTMS and high suicide risk	*Age, mean yrs* G1: 47.2 G2: 48.5 G3: 51.1 *Sex, % females* G1: 70 G2: 40 G3: 40 *Race, % white* NR *Right handed, %* G1: 90% G2: 100% G3: 100% *HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10 Baseline score, mean (SD) G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14) *CGI-S* Baseline n G1: 10 G2: 10 G3: 10	G3: 18.10 (6.15) Follow up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0) Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%) At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), *P* = 0.048 Follow up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%) G1: vs. G2+G3, *P* = 0.121 Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) *P* = NR *CGI-S* Endpoint score, mean (SD)	pharmacotherapy At end of treatment, % G1: 0 G2: 0 G3: 0 At end of followup, % NR Does not report which group 3 patients came from Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions ofbrain after examination with single photon emission computed tomography (20-Hz rTMS to an area of relatively low activity and 1-Hz rTMS to an area showing relatively high activat *Adherence/ compliance* Compliance all patients completed active 2 week treatment

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	1800 • Total number of sessions: 10 in 2 wks High • Frequency (Hz):20 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval: 20+5 • Pulses per session: 1200 • Total number of sessions: 10 in 2 wks Sham • Same but with coil angling 45 degrees away from scalp		Baseline score, mean (SD) G1: 4.7 (0.82) G2: 4.8 (1.0) G3: 4.8 (0.63)	At 2 weeks G1: 4.6 (0.97 G2: 3.8 (1.48) G3: 3.9 (0.99) 2 week follow up G1: 4.75 (1.16) G2: 4.00 (1.15) G3: 3.7 (1.57)	
Author, Year George, 2010[18] *Country, setting* United States, outpatient *Funding* NIMH as the Optimization of TMS for the Treatment of Depression Study	*Study design* RCT *Type of analysis* mITT (all randomized patient who started at least 1 treatment session) Completer (randomized patients who were treated according ot protocol and had fewer than 4	*TRD definition* • Moderate level of treatment resistance as defined by the ATHF; insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥ 3 trials; Author personal communication states, "All patients had either one failed antidepressant failure,	*Subgroups* No Subgroups *Baseline n* mITT G1: 92 G2: 98 *Treatment Failure* Failed 1 or more, % G1: NR G2: NR	*HAM-D (Insert #)* Yes HAMD24 G1:rTMS G2: Sham N Analyzed mITT G1: 92 G2: 98 Observed: G1: 92 G2: 98	*Quality of Life* No *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Research Objective To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder *Quality Rating* Good	rescheduled, missed, or partially completed rTMS sessions dueing weeks 2 to 6) Fully Adherent (fewer than 2 rescheduled, missed, or partially complete sessions; must not have been taking prohibited psychiatric medications or illicit drugs; and had no other protocol violations) *N* Randomized: 199 ITT: 190 Completers: 154 Adherent: 120 *Duration* Fixed Duration Active Treatment: 3 wks Variable Duration Active Treatment: 3 wks No-treatment lead-in: 2 wks HAM-D assessment performed twice weekly Acute trial terminated when patients met the stable remission criteria.	or multiple intolerance to antidepressant medications." • Not required in the current episode *Tier 2* *Inclusion criteria* • Antidepressant medication-free outpatients; 18-70 yo; DSM-IV MDD, single or recurrent; HAM-D24 ≥ 20; Stable during 2wk medication-free lead-in; moderate level of treatment resistance as defined by the Antidepressant Treatment History Form (ATHF); insufficient clinical benefit to 1-4 adequate medication trials or intolderant to ≥ 3 trials. *Exclusion criteria* • Other current Axis I disorders; past failure to respond to an adequate trial of ECT; prior treatment with TMS or VNS; personal or close family history or seizure disorder; Neurologic disorder;	Failed 2 or more, % G1: NR G2: NR Current episode failures, mean Mean, median (SD) G1: 1.62, 1 (1.37) G2: 1.41, 1 (0.97) Mean failed trials Mean, median (SD) G1: 3.34, 2 (2.68) G2: 3.28, 3 (2.11) *Polarity, %* Unipolar G1: 100 G2: 100 Bipolar I G1: 0 G2: 0 Bipolar II G1: 0 G2: 0 *Patient Characteristics* *Age, mean yrs* G1: 47.7 G2: 46.5 *Sex, % females* G1: 63	Observed Endpoint: G1: 83 G2: 91 Completers: G1: 72 G2: 82 Fully Adherent: G1: 57 G2: 63 Endpoint score, mean (SD) Observed G1: 21.61 (9.26) G2: 23.38 (7.43) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -4.23 to 0.10, -0.42, p = 0.06 Change, mean (SD) Observed at 3 weeks G1: -4.65 (NR) G2: -3.13 (NR) Responders, n mITT: G1: 14 G2: 5 p = 0.009 OR of responding to rTMS vs. Sham 4.6 (95%CI, 1.47 to 14.42) Completer:	Cognitive impairment, % NR Dizziness, % NR Headache, % G1: 32 G2: 23 Insomnia, % G1: 7.6 G2: 10 Post op complications, % NR Somnolence, % G1: 5 G2: 4 Suicidality, % Suicidality: NR Suicides: G1: 0 G2: 0 Additional Comments Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	Interventions rTMS Sham G1: rTMS G2: Sham G1: rTMS G2: Sham G1:rTMS G2: Sham *Medications Allowed* None (2 week washout) *Strategy* Switch strategy *Parameters* G1: Location: Left prefrontal cortex Frequency: 10 Hz Intensity 120% MT Pulses: 10 pulses per second for 4 seconds; 3000 persession Intertrain interval: 26 seconds Length of Session: 37.5 minutes (75 trains) Fixed Active Treatment - Number of sessions: daily weekday sessions (15 sessions) Blinded treatment for improvers - Number of sessions: daily	Ferromagnetic material in body or close to head; pregnancy; taking meds known to lower seizure threshold.	G2: 51 *Race, % white* G1: NR G2: NR *Not Specified, %* G1: NR G2: NR *Right handed, %* G1: NR G2: NR *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) G1: 26.3 (5.0) G2: 26.5 (4.8) *BDI* *Baseline score, mean (SD)*	G1: 10 G2: 4 p = 0.02 Fully Adherent: Overall = 7 p = 0.14 Remitters, n No. (95%CI) mITT: G1: 13 (8.5 to 22.7) G2: 5 (2.3 to 11.4) OR (95%CI): 4.18 (1.32 to 13.24) Completers: G1: 10 (7.8 to 23.7) G2: 4 (2.0 to 11.9) OR (95%CI): 4.92 (1.29 to 18.76) Fully Adherent: G1: 6 (5.0 to 21.2) G2: 2 (1.0 to 10.8) OR (95%CI): NS Remitters by Treatment Phase Phase I Fixed(Wks 1-3) G1: 6 G2: 2 Phase I Variable (Wks 4-6) Week 4 Day 2 G1: 2 G2: 0 Week 4 Day 5 G1: 3 G2: 0 Week 5 Day 2	Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient *Neuropsychological or executive functioning* No Measures, Results NA

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	weekday sessions for up to another three weeks (total possible sessions = 30) G2: Similar coil as active treatment witha metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.			G1: 2 G2: 3 Other Response: ≥ 50% decrease in HAM-D score from baseline) Remission: HAM-D score of 3 or less or 2 consecutive Ham-D scores less than 10 *MADRS* Yes G1: rTMS G2: Sham Baseline n Observed Baseline G1: 92 G2: 98 Observed End of Phase I G1: 83 G2: 91 Baseline score, mean (SD) G1: 29.5 (6.9) G2: 29.8 (6.4) Endpoint score, mean (SD) Observed at 3 weeks G1: 24.59 (11.44) G2: 27.75 (9.06) G1: vs. G2, 95% CI	Predefined No MMSE No Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other *Other* Yes Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%):

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
				Effect Estimate, Cohen d, p-value: -6.10 to -0.76, -0.51, p = 0.01 Change, mean (SD) Observed at 3 weeks G1: -4.89 (NR) G2: -2.06 (NR) Responders, n NR Remitters, n NR Other NA IDS Yes G1:rTMS G2: Sham[Q60] Baseline n Observed Baseline: G1: 86 G2: 94 Observed at end of Phase I: G1: 78 G2: 88 Baseline score, mean (SD)	G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient Adequate information Yes *Attrition* Overall, % All attrition calculations based on mITT 10.5% At end of treatment, % G1: 12 G2: 9 At end of followup, % G1: NA G2: NA

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
				G1: 41.0 (9.3) G2: 40.1 (9.8) Endpoint score, mean (SD) Observed at 3 weeks G1: 32.56 (15.40) G2: 36.70 (13.91) G1: vs. G2, 95% CI, Cohen d, p-value: -10.04 to -2.62, -0.66, p = 0.001 Change, mean (SD) Observed at 3 weeks G1: -8.42(NR) G2: -3.37 (NR) Responders, n NR Remitters, n NR Other NA *CGI-S* Yes G1: rTMS G2: Sham Baseline n Observed at baseline: G1: 90 G2: 98 Observed at end of Phase I:	Withdrawals due to efficacy, % G1: NR G2: NR Withdrawals due to adverse events, % G1: 5.4 G2: 0 Other *Adherence/ compliance* Adherence Fully Adherent n= 120 G1: n = 57 G2: n = 63

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
				G1: 82 G2: 90 Baseline score, mean (SD) G1: 4.62 (0.70) G2: 4.63 (0.69) Endpoint score, mean (SD) Observed at 3 weeks G1: 3.96 (1.14) G2: 4.30 (0.87) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -0.68 to -0.09, -0.55, p = 0.01 Change, mean (SD) Observed at 3 weeks G1: -0.66 (NR) G2: -0.33(NR) Other NA	
Author, Year Holtzheimer et al., 2004[19] *Country, setting* USA, single center, outpatient/inpatient status not clearly stated *Funding*	*Study design* RCT *Type of analysis* ITT *N* 15 *Duration* Primary endoint	*TRD definition* • Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in	*Treatment Failure* Failed 7 or more, % G1: 85.7 G2: 37.5 *Polarity, %* Unipolar 100% MDD *Age, mean yrs*	*HAM-D 17* Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7) At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)	*Quality of Life* NR *Adverse Events* No major adverse events at any point in study. Some subjects experienced mild pain withactive rTMS, but treatments were generally well tolerated.

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
University of Washington *Research Objective* Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable *Quality Rating* Fair	following 2 weeks of treatment and follow up 1 week after txt completed *Interventions* G1: rTMS G2: Sham *Medications Allowed* All pts discontinued (failed) AD medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5 • Inter-train interval: 30-60 • Pulses per session: 1600 • Total number of sessions: 10 over 2 wks Sham rTMS • Delivered in same anatomical location with identical	current episode *Tier 1* *Inclusion criteria* • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18 *Exclusion criteria* • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy	G1: 40.4 G2: 45.4 *Sex, % females* G1: 57.1 G2: 42.9 *Right handed, %* G1: 100 G2: 100 *HAM-D 17* Baseline n G1: 7 G2: 8 Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3) *BDI* Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)	1 week follow up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8 At week 2 G1: 8.1 G2: 5.5 1 week follow up G1: 3.9 G2: 3.2 All endpoints, *P* = NS Responders, n (%) At week 1 G1: 0 G2: 0 At week 2 G1: 2 (28.6) G2: 1 (12.5) 1 week follow up G1: 0 G2: 0 *BDI* Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7) At week 2	*Neuropsychological or executive functioning* Both groups performed equally well withexception of one measure of verbal memory, Trial 7 ofRey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); *P* < 0.05). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions. MMSE NR There were no major adverse events at any point instudy. Some subjects experienced mild pain withactive rTMS, but treatments were generally well tolerated. *Attrition* Overall, % 0 during treatment. 3 (20%) beforefinal assessment at week 3 At end of treatment, % 0

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp			G1: 23.9 (2.6) G2: 22.4 (2.4) 1 week follow up G1: 23.9 (1.6) G2: 26.4 (1.9) Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1 Change, mean (SD) 1 week follow up G1: -5.7 G2: -2.1 Group x time (all points), *P* = NS	At end of followup, % G1: 28.6 G2: 12.5 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR *Adherence/ compliance* Compliance All 15 subjects completed all 10 txt sessions
Author, Year Kauffmann et al., 2004[20] *Country, setting* NR, NR – investigators for the US *Funding* Not reported *Research Objective* Assessefficacy of right prefrontal slow repetitive rTMS in TRD pts *Quality Rating*	*Study design* RCT *Type of analysis* ITT *N* 12 *Duration* 10 treatments over 2 weeks Primary Outcome: Change in HAM-D/Response after 10 sessions *Interventions*	*TRD definition* • 2+ failed AD trials (8+ weeks at adequate doses) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* Major Depression (DSM-IV) age 18+ *Exclusion criteria* Preexisting neurological and/or	*Treatment Failure* Mean failed trials NR: *Polarity, %* 100% Major Depression *Age, mean yrs* Overall 51.7 *Sex, % females* Overall 91.7 *HAM-D 21* Baseline n G1: 7 G2: 5	*HAM-D 21* Endpoint score, mean (SEM) G1: 11.29 (3.17) G2: 11.80 (1.93) Change, mean (SD) G1: -10.57 G2: -6.31 *P* = NR (ns) Responders, n G1: 4 (57%) G2: 2 (40%) Response2, n HAM-D21 <10 G1: 4 (57%) G2: 1 (20%)	*Quality of Life* NR *Adverse Events* NR Additional Comments There were "No AEs reported" "there were no adverse events" *Neuropsychological or executive functioning* No Measures, Results NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Fair	G1: rTMS G2: Sham *Medications Allowed* allowed to continue antidpressants but advised to discontinue benzodiazepines & mood stablizers *Strategy* Augmentation *Parameters* rTMS • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 2 • Length of train (seconds): 60 • Inter-train interval: 180 • Pulses per session: 120 • Total number of sessions: 10 in 10 days Sham • Same as above but coil was held at a 45 degree angle from skull	cardiac diseases	Baseline score, mean (SEM) G1: 21.86 (2.31) G2: 18.20 (2.20)	*Relapse* On follow up most pts in txt group relapsed after 2-3 month, whereas pts in sham group who improved relapsed in 2 weeks	Predefined Yes MMSE NR *Other* Yes "there were no adverse events" Adequate information No *Attrition* Overall, % 0 At end of treatment, % NR At end of followup, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					Adherence/ compliance NR NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Author, Year Padberg et al., 1999[21] *Country, setting* Germany, university clinic, patient status not clear *Funding* Magstim Company Ltd. & Micromed Medizin-Elektronik GmbH *Research Objective* Compare antridepressant efficacy and tolerability of fast, slow, and sham rTMS in TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 18 *Duration* 1 week of active txt Primary outcome: Change in HAM-D after 5 txt sessions *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: High rTMS G2: Low rTMS G3: Sham rTMS *Medication allowed* 83.3% of pts continued on their current [failed] AD medication,others were not on a med and did not start one prior to trial *Strategy* Augmentation *Parameters* rTMS High	*TRD definition* • 2+ failed txt trials of 4+ wks duration including at least one tricyclic • Required to be in current episode *Tier 1* *Inclusion criteria* MDD (DSM IV) *Exclusion criteria* organic brain disorders, contraindications for rTMS	*Treatment Failure* Current episode failures, mean G1: 4.0 (2.2) G2: 3.2 (0.8) G3: 3.2 (1.2) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 63.5 G2: 46.7 G3: 43.3 *Sex, % females* G1: 33.3 G2: 83.3 G3: 66.7 *Right handed, %* G1: 100 G2: 100 G3: 100 *HAM-D 21* Baseline n G1: 6 G2: 6 G3: 6	*HAM-D 21* Endpoint score, mean (SD) G1: 28.5 (9.4) G2: 21.5 (21.5) G3: 23.5 (10.4) Change, mean (SD) G1: -1.7 G2: -5.2 G3: -1.3 $P > 0.05$ Responders, n NR Remitters, n NR *MADRS* Endpoint score, mean (SD) graph only Group x time, $P < 0.1$	*Quality of Life* NR *Adverse Events* Headache, % G1: 16.7 G2: 16.7 G3: NR Focal Pain at rTMS site during stimulations: 50%, 33.3%, & 0%. There were no serious AE. *Neuropsychological or executive functioning* Verbal Memory Tests (included 3 learning trials and a consecutive, delayed recall task after distraction): Verbal memory performance improved significantly after fast rTMS Learning 1. $P = 0.006$ 2. NA 3. Fast rTMS improvement $P = 0.032$, Slow rTMS P = NS, Sham decrease in performance $P = 0.09$ *MMSE* NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	• Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 5 • Length of train (seconds): 5 • Inter-train interval: 30 • Pulses per session: 250 • Total number of sessions: 5/wk rTMS Low • Frequency (Hz):0.3 • Motor threshold (%): 90 • Number of trains: 10 • Length of train (seconds): 25 • Inter-train interval: NR • Pulses per session: 75 • Total number of sessions: 5/wk Sham: • Same as high rTMS except coil angled at 90 degrees with 1 wing resting on skull		Baseline score, mean (SD) G1: 30.2 (9.5) G2: 26.7 (9.4) G3: 22.2 (8.8) *MADRS* Baseline n G1: 6 G2: 6 G3: 6 Baseline score, mean (SD) graph only		*Attrition* Overall, % NR, "no pts asked for discontinuation of rTMS" At end of treatment, % NR At end of followup, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR - "compliance was excellent"

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Author, Year Pallanti et al., 2010[22] Pallanti *Country, setting* Italy Single Center Outpatient *Funding* Italian Department of Health *Research Objective* Compare unilateral low frequency, sequential bilateral rTMS treatment and sham in pts with TRD under stable pharmacological treatment *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell *N* 60 *Duration* Active treatment: 3 wks Primary outcome measure: HAMD measured weekly *Interventions* Unilateral rTMS Bilateral rTMS Sham G1: Bilateral Stimulation G2: Unilateral Stimulation G3: Sham *Medications Allowed* Current [failed] antidepressant regime continued *Strategy* Augment or add-on strategy	*TRD definition* • Failed two or more adequate (6 weeks or more each) treatments. • Not required to be in current episode *Tier 1* *Inclusion criteria* • Right-handed; ≥ 18 yrs; HAM-D score ≥ 18; ≥ 2 failed AD trials (≥ 6 wk duration); duration ≥ 4mos for current depressive episode; illness duration ≥ 4 yrs. *Exclusion criteria* • Any additional psychiatric comorbidity; rTMS contraindications (metallic implants, foreign bodies, history of seizures); major medical disease; inability or refusal to provide written informed consent.	*Subgroups* No Subgroups *Baseline n* G1: 20 G2: 20 G3: 20 *Treatment Failure* Failed 1 or more, % G1: 100 G2: 100 G3: 100 Failed 2 or more, % G1: 100 G2: 100 G3: 100 Current episode failures, mean G1: NR G2: NR G3: NR Mean failed trials No. of previous adequate courses of medication failed: mean (SD, 95%CI) G1: 5.90 (1.48 , 5.21-6.59) G2: 6.50 (1.48, 5.21-6.59) G3: 5.95 (1.67, 5.72-7.28)	*HAM-D (Insert #)* Yes HAM-D17 G1: Bilateral Stimulation G2: Unilateral Stimulation G3: Sham Endpoint score, mean (SD) NR Change, mean (SD) NR Responders, n HAM-D reduction up to 10% G1: 5 G2: 4 G3: 15 $\chi 2$ 19.17, df 6, Sig. = 0.04 HAM-D reduction up to 25% G1: 5 G2: 6 G3: 3 HAM-D reduction up to 50% G1: 6 G2: 3 G3: 0 HAM-D reduction over 50% G1: 4 G2: 7	*Quality of Life* No *Adverse Events* Overall, % G1: NR G2: NR G3: NR Amnesia, % G1: NR G2: NR G3: NR Cardiovascular adverse events, % G1: NR G2: NR G3: NR Cognitive impairment, % Week 0 G1: 25 G2: 20 G3: 35 Week 3 G1: 15 G2: 10 G3: 30 Dizziness, % Week 0 G1: 5 G2: 0 G3: 0 Week 3 G1: 0

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	Parameters G1: Bilateral: Location of Stimuli: 1st applied of right DLPFC then left DLPFC Right DLPFC Frequency: 3 140s trains at 1 Hz Intensity: 110% RMT Interval: 30s intertrain interval Total 420 stimuli per session Left DLPFC Frequency: 20 5s trains at 10 Hz Intensity: 100% RMT Interval: 25 s intertrain interval Total 1000 styimuli per session G2: Unilateral: Location of Stimuli: Right DLPFC Frequency: 3 140s trains at 1 Hz Intensity: 110% RMT Interval: 30s intertrain interval Total 420 stimuli per session Sham: Left DLPFC Same length of time as the 420 stimuli per session.		*Polarity, %* Unipolar G1: 100 G2: 100 G3: 100 Bipolar I G1: NR G2: NR G3: NR Bipolar II G1: NR G2: NR G3: NR *Patient Characteristics* *Age, mean yrs* G1: 47.60 G2: 51.20 G3: 47.85 *Sex, % females* G1: 55 G2: 60 G3: 60 *Race, % white* G1: NR G2: NR G3: NR *Not Specified, %* G1: NR G2: NR G3: NR	G3: 2 NNT (Response) rTMS1 vs. sham 10.00 (95%CI: 3.13 to -8.39) rTMS2 vs. sham 4.00 (95%CI: 2.01 to 328.11) Remitters, n G1: 2 G2: 6 G3: 1 χ2 5.49, df 2, Sig. = 0.064 NNT (Remission) rTMS1 vs. sham 20.00 (95%CI: 4.71 to -8.89) rTMS2 vs. sham 4.00 (95%CI: 2.12 to 36.23) Other Remission: HAM-D < 8	G2: 0 G3: 0 Headache, % Week 0 G1: 40 G2: 30 G3: 20 Week 3 G1: 5 G2: 5 G3: 5 Insomnia, % G1: NR G2: NR G3: NR Post op complications, % G1: NR G2: NR G3: NR Somnolence, % G1: NR G2: NR G3: NR Suicidality, % G1: NR G2: NR G3: NR Additional Comments Not including previously listed Aes Pain/burning in the scalp:

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	Carried out with the MAGSTIM placebo coil system.		*Right handed, %* G1: 100 G2: 100 G3: 100 *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) Score (SD, 95%CI) G1: 28.75 (6.01, 25.93-31.57) G2: 27.95 (5.89, 25.19-30.71) G3: 29.05 (3.54, 27.39-30.71)		Week 0 G1: 50 G2: 40 G3: 15 Week 3 G1: 5 G2: 0 G3: 10 Anxiety Week 0 G1: 20 G2: 15 G3: 15 Week 3 G1: 0 G2: 0 G3: 5 Seizure Episode Week 0 G1: 0 G2: 0 G3: 0 Week 3 G1: 0 G2: 0 G3: 0 *Neuropsychological or executive functioning* No Measures, Results NR Predefined Collection method not reported

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					MMSE No Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other *Other* Yes Not including previously listed Aes Pain/burning in the scalp: Week 0 G1: 50 G2: 40 G3: 15 Week 3 G1: 5 G2: 0 G3: 10 Anxiety Week 0 G1: 20 G2: 15 G3: 15 Week 3 G1: 0 G2: 0 G3: 5 Seizure Episode Week 0

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					G1: 0 G2: 0 G3: 0 Week 3 G1: 0 G2: 0 G3: 0 Adequate information No *Attrition* Overall, % NR Text states, "none left the study due to pain at the stimulation site" At end of treatment, % G1: NR G2: NR G3: NR At end of followup, % G1: NR G2: NR G3: NR Withdrawals due to efficacy, % G1: NR G2: NR G3: NR Withdrawals due to adverse events, % G1: 0

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					G2: 0 G3: 0 Text states, "none left the study due to pain at the stimulation site" Other *Adherence/ compliance*
Author, Year Pascual-Leone et al., 1996[23] *Country, setting* Spain, both inpatients and outpatients *Funding* Generalitat Valenciana andSpanish Minsterio de Educacion y Ciencia *Research Objective* To study effects of focal rTMS on depressive symptoms of 17 patients with medication-resistant depression of psychotic subtype. *Quality Rating* Fair	*Study design* RCT, Cross-over trial *Type of analysis* ITT *N* 17 *Duration* Primary endpoint after 1 week of treatment. Total study duration 5 months (3 week washout between treatments) *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: High Freqency rTMS G2: High frequency right rTMS (control)	*TRD definition* • At least three episodes of depression that had been resistant to multiple medications despite combinations and high doses *Tier 1* *Inclusion criteria* • Right-handed; • Diagnosed with major depression, psychotic subtype (DSM-III-R) • history of relapsing unipolar major depression • Met safety criteria for rTMS • normal neurological and general physical examinations *Exclusion criteria* • History of bipolar	*Subgroups* Psychosis *Treatment Failure* Mean failed trials Overal: NR *Polarity, %* Unipolar Overall: 100 *Age, mean yrs* Overall: 48.6 *Sex, % females* Overall: 59% *Right handed, %* Overall: 100 *HAM-D 21* Baseline n Overall: 17(cross-over study, all patients received all	*HAM-D 21* Endpoint score, mean (SD) G1: 13.8 G2: NR G3: NR G4: NR G5: NR Change, mean (SD) G1: -11.4 G2: NR G3: NR G4: NR G5: NR *P* < 0.001 G1: vs. All controls, *P* < 0.0005 *BDI* Endpoint score, mean (SD) G1: 25.7 G2: NR G3: NR	*Quality of Life* NR *Adverse Events* Overall, % G1: 41% G2: Amnesia, % G1: NR G2: Cardiovascular adverse events, % G1: NR G2: Cognitive impairment, % G1: NR G2: Dizziness, % G1: NR G2:

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	G3: Sham left rTMS G4: Sham right rTMS G5: Real vertex stimulation (control) *Medications Allowed* Attempts were made to taper medications. Nine patients continued AD medication and only 4 patients were AD free at the end of the study. All pts given nimodipine at a constant dose of 30mg/3x daily *Strategy* Mixed-within group differences *Parameters* • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 10 • Inter-train interval: 60 • Pulses per session: 2000 • Total number of sessions: 5 in 5days • Left Sham Coil angeled at 45 degrees with edge of coil	disorder • History of brain surgery or epilepsy • Concurrent serious medical illnesses requiring long-term treatment; • Previously received rTMS	interventions) Baseline score, mean (SD) G1: 25.2 G2: NR G3: NR G4: NR G5: NR BDI Baseline score, mean (SD) G1: 47.9 G2: NR G3: NR G4: NR G5: NR	G4: NR G5: NR Change, mean (SD) G1: -22.2 G2: NR G3: NR G4: NR G5: NR *P* < 0.0001 G1: vs. All controls, *P* < 0.0005	 Headache, % G1: NR G2: Insomnia, % G1: NR G2: Post op complications, % G1: NR G2: Somnolence, % G1: NR G2: Suicidality, % G1: NR G2: Additional Comments Study does not report how A.E.s were reported or elicited. It does state that all pts tolerated rTMS without complications; No seizure induced. Seven pts complained about minor headaches that were not related tostimulation condition. *Neuropsychological or executive functioning* No

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	resting on scalp • Right Sham Coil angeled at 45 degrees with edge of coil resting on scalp				Measures, Results NR Predefined No MMSE NR *Other* Yes Study does not report how A.E.s were reported or elicited. It does state that all pts tolerated rTMS without complications; No seizure induced. Seven pts complained about minor headaches that were not related tostimulation condition. Adequate information No *Attrition* Overall, % NR At end of treatment, % G1: NR G2: At end of followup, % G1: NR G2:

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2: Other The authors report, "All patients tolerated rTMS without complications…complications were not related to stimulation condition and did not prompt pts to request discontinuation ofstudy." *Adherence/ compliance* NR
Author, Year Rush et al., 2005[24] Carpenter et al., 2004[25] *Country, setting* US, multicenter, outpatient psychiatric *Funding* Cyberonics, Inc. *Research Objective* To compare adjunctive VNS to sham in TRD	*Study design* RCT *Type of analysis* m-ITT/P*P* for efficacy, ITT for Aes *N* 235 *Duration* 10wks of stimulation Primary Outcome: HAM-D Response after	*TRD definition* • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode *Tier 1* *Inclusion criteria* • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+	*Treatment Failure* Percent with 4-6 current episode failures G1: 46.5% G2: 40.0% *Polarity, %* Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6	*HAM-D24* N analyzed G1: 112 G2: 110 Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) *P* = 0.639 Responders, n G1: 17 (15.2%)	*Quality of Life* Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis Baseline score, mean (SD) NR Endpoint score, mean (SD) NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
patients *Quality Rating* Good	10wks txt Interventions G1: VNS G2: Sham *Medications allowed* pts allowed up to 5 antidepressants, mood stablizers, or other psychotropic medications *Strategy* Augmentation *Parameters* VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs • On/Off cycle parameters: 30 sec on and 5 min off • Duration of treatment: Sham: • Device implanted but not turned on	MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium *Exclusion criteria* • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disoder, suicidality • risks related to surgical implantation	Bipolar II G1: 6.3 G2: 5.5 Age, mean yrs G1: 47.0 G2: 45.9 Sex, % females G1: 59 G2: 66 Race, % white G1: 97 G2: 96 *HAM-D24* Baseline n G1: 119 G2: 116 Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2) *MADRS* Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3) *IDS* Baseline n G1: 112 (115 randomized) G2: 110 Baseline score, mean (SD) G1: 44.3(9.1)	G2: 11 (10.0%) *P* = 0.251 *MADRS* Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) *P* = 0.208 Responders, n G1: 17 (15.2) G2: 12 (0.0) *P* = 0.378 *IDS* Endpoint score, mean (SD) NR % change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) *P* = 0.158 Responders, n G1: 19 (17) G2: 8 (7.3) *P* = 0.032 Remitters, n NR *CGI-I* Endpoint score, mean (SD) NR	Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2) Other Physical component between VNS and sham: *P* = 0.480, Mental Component between VNS and sham: *P* = 0.406 *Adverse Events* Overall, % NR Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:– • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%,

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
			G2: 45.4(8.5) *CGI-I* Baseline n G1: 112 G2: 110	 Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, *P* = 0.648	 • hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11 patients, were cases of worsening depression requiring hospitalization Cardiac SAEs during implantation: 1.7% v 0% COSTART used to code reported events *Attrition* Overall, % 1.3 (3/235) At end of treatment, % G1: 2.6 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, %

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					G1: 2.6 G2: 0 9 pts had a protocol violation post randomization *Adherence/ compliance* NR
Author, Year Su et al., 2005[26] *Country, setting* Taiwan, NS *Funding* Taipei Veterans General Hospital, patient status not reported *Research Objective* To investigate whether two weeks of rTMS applied toLDLPFC can alleviate TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 33 *Duration* 2wk of active txt Primary outcome: HAM-D at 2 weeks (after 10 txt) *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: 20Hz rTMS (N analyzed = 10) G2: 5Hz rTMS (N analyzed = 10) G3: Sham (N analyzed = 10) *Medications allowed* pts allowed to continue	*TRD definition* • TRD (2+ failed adequate trials) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major Depressive Episode or Bipolar (DSV-IV), • Ham-D21 score >=18 *Exclusion criteria* • history of - epilepsy, • any physical and neurological abnormalities, major head trauma, • psychotic symptoms; • current us of a pacemaker, • suicidality	*Subgroups* Ethnicity - Chineese, females by menopausal status *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar G1: 90 G2: 80 G3: 80 Bipolar G1: 10 G2: 20 G3: 20 Bipolar II G1: 10 G2: 10 G3: 10 Age, mean yrs G1: 43.6 G2: 43.2 G3: 42.6 Sex, % females G1: 70 G2: 80	*HAM-D 21* N analyzed G1: 10 G2: 10 G3: 10 Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 12.3(7.7) G3: 19.0(7.7) Change, mean (SD) At 2 weeks G1: -13.4(4.9) G2: -14.2(6.0) G3: -3.7(9.3) G1: vs. G3, G2 vs. G3 *P* < 0.01 Responders, n G1: 6 (60) G2: 6 (60) G3: 1 (10) G1: + G2 vs. G3 *P* = 0.01 Remitters, n Ham-D17<= 7	*Quality of Life* NR *Adverse Events* Headache, % G1: 20 (n=2) G2: 20 (N=2) G3: 11.1 (N=1) Pain at rTMS site: 16.7% withdrew due to pain at stimulation site SEE AE section *Attrition* Overall, % 9.1 (3/33) At end of treatment, % G1: 0 G2: 16.7 G3: 9.1 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 0 G3: 9.1

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	all meds constant for 4 weeks prior (e.g. antidepressants, antipsychotics, mood stablizers, or stimulant *Strategy* Augmentation *Parameters* rTMS High: • Frequency (Hz): 20 • Motor threshold (%): 100 • Number of trains:40 • Length of train (seconds):2 • Inter-train interval:28 • Pulses per session: 1600 • Total number of sessions: 5/wk or 10 in 10 weekdays rTMS Low: • Frequency (Hz): 5 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 8 • Inter-train interval: 22 • Pulses per session: 1600 • Total number of sessions:5/wk or 10 in 10 days		G3: 70 HAM-D 17 Baseline N G1: 10 G2: 12 G3: 11 Baseline score, mean (SD) G1: 23.2 (7.5) G2: 26.5 (5.2) G3: 22.7 (4.7) *BDI* Baseline score, mean (SD) G1: 28.0(9.1) G2: 33.9(7.6) G3: 33.4(9.6) *CGI-S* Baseline score, mean (SD) G1: 4.5(0.7) G2: 4.7(0.8) G3: 4.7(0.48)	G1: 5 (50) G2: 5 (50) G3: 0 *BDI* Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 19.7(12.3) G3: 28.7(15.1) Change, mean (SD) At 2 weeks G1: 15.2(7.5) G2: 14.2(10.4) G3: 4.7(9.1) G1: vs. G3 *P* <0.05 G2 vs. G3 *P* <0.1 *CGI-S* Endpoint score, mean (SD) At week 2 G1: 2.8(1.1) G2: 2.0(0.9) G3: 3.6(1.1) Change, mean (SD) G1: -1.7 G2: -2.0 G3: -1.1 *P* = NS	Withdrawals due to adverse events, % G1: 0 G2: 16.7 G3: 0 1 dropped out of sham for worsening of clinical symptoms, this was categorized as LOE *Adherence/ compliance* NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	Sham: • Same as high frequency rTMS. Coil placed at 90 degrees off skull.				
Author, Year Zheng et al., 2010[27] *Country, setting* China, Single Center, inpatient/outpatient setting not clearly reported *Funding* National Natural Science Foundation of China (30830046 to Lingjiang Li), the National Science and Technology Program of China (2007BAI17B02 to Lingjiang Li), the National 973 Program of China (2009CB918303, 2007CB512308 to Lingjiang Li and Zhang Zhijun); Program of Chinese Ministry of Education (20090162110011 to Lingjiang Li);NationalHi-Tech Research and Development Program	*Study design* RCT *Type of analysis* Cannot tell *N* 34 *Duration* 4 weeks *Interventions* G1: rTMS G2: Sham *Medications Allowed* Augment – all patients taking escitalopram from 2+ weeks before trial *Strategy* Augment or add-on strategy *Parameters* rTMS - 20 sessions of rTMS over the left DLPFC within four weeks, at 110% stimulation intensity	*TRD definition* • failure to respond to at least two different antidepressants given for a period longer than 4 weeks at the maximum recommended dose. • Not required to be in current episode *Tier -1* *Inclusion criteria* • Fulfilling the diagnostic criteria for major depressive episode (DSM-IV) and referred for rTMS because of drugtreatment resistance were enrolled in this study. • Age of the patients was from 18 to 37 years *Exclusion criteria* • Any other psychiatric axis-I or axis-II disorders	*Subgroups* Young adults (18-37) *Baseline n* G1: 19 G2: 15 *Treatment Failure* Failed 1 or more, % 100 Failed 2 or more, % 100 Current episode failures, mean NR Mean failed trials NR *Polarity, %* Unipolar 100 *Patient Characteristics* *Age, mean yrs* G1: 26.9 G2: 26.7 *Sex, % females*	*HAM-D (17)* Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 22.9 (3.4) Change, mean (SD) G1: -11.1 G2: -1.7 *P* = NR Responders, n G1: 12 G2: 1 Remitters, n NR Other Responders - Fisher's exact test, *P* < 0.001 *BDI* Yes G1: rTMS G2: Sham Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 19.8 (5.1)	*Quality of Life* NR *Adverse Events* NR *Neuropsychological or executive functioning* NR *MMSE* NR *Other* NR *Attrition* NR *Adherence/ compliance* NR

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
of China (863 program: 2008AA02Z413 to Zhang Zhijun) *Research Objective* To assess metabolic changes within prefrontal cortex after rTMS treatment *Quality Rating* Fair	related to resting motor threshold	• History of epileptic seizures or any other neurological disorder • Any kind of metal implants • Any other clinically relevant abnormalities in their medical history or laboratory examinations • Medical history of alcohol or drug abuse	G1: 36.8 G2: 33.3 *Race, % white* NR *Not Specified, %* NR *Right handed, %* NR *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) G1: 24.6 (3.0) G2: 24.6 (2.8) *BDI* Baseline score, mean (SD) G1: 21.1 (4.2) G2: 21.0 (4.2)	Change, mean (SD) G1: -7.6 G2: -1.2 Responders, n NR Remitters, n NR	

Evidence Table 5. KQ1 active versus control: Tier 2

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Berman et al., 2000[28] *Country, setting* US, urban community health center, inpatient and outpatients *Funding* Veterans Administration, NIMH, State of CT *Research Objective* To assessefficacy of rTMS in unmedicated TRD patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 20 *Duration* 2 weeks (10 weekdays of txt) Primary outcome = HAM-D at 2wks Interventions G1: rTMS G2: Sham TMS *Medications Allowed* All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep *Strategy* Switch *Parameters* rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imiprimine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode *Tier 2* *Inclusion criteria* • Current Major depressive episode (via Ham-D) *Exclusion criteria* • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control	*Treatment Failure* Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup) *Polarity, %* Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 Age, mean yrs G1: 45.2 G2: 39.4 Sex, % females G1: 20 G2: 40 Race, % white G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic) *HAM-D 25* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 37.1 G2: 37.3	*HAM-D 25* G1: rTMS G2: Sham TMS Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) *P* < 0.01 Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 *P* = 0.09 Three partial responders symptom severity returned to baseline within 1-2 weeks *BDI* Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) *P* = 0.27	*Quality of Life* NR *Adverse Events* Headache, n G1: 60 G2: 50 Difficulty starting urination great in active group *P* = 0.03 Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appétit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days Sham • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp				coordination, and muscle stiffness *MMSE* NR *Attrition* Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0 *Adherence/ compliance* NR
Author, Year Manes et al., 2001[29] Includes additional neuro-psychological outcomes reported in Moser et al., 200230 *Country, setting* US, outpatient clinic	*Study design* RCT *Type of analysis* cannot tell if ITT *N* 20	*TRD definition* • Not required or not specified to be in current episode *Setting(s)* Outpatient Psychiatric	*Subgroups* Age 50+ *Treatment Failure* Mean failed trials G1: 4 (2.3) G2: 4 (1.2)	*HAM-D* Endpoint score, mean (SD) At 1 week G1: 13.7 (5.4) G2: 16.2 (8.5) 1 week Follow-up G1: 14.4 (6.4) G2: 15.5 (9.1)	*Quality of Life* NR *Adverse Events* Headache, % G1: 40% G2: 0% Other:

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Funding NIMH *Research Objective* To examineantidepressant efficacy of rTMS in a TRD population *Quality Rating* Fair	*Duration* 2 weeks (1 week of treatment, 1 wk follow-up following last treatment) Primary outcomes HAM-D at end of treatment and at 1 week follow-up Interventions G1: rTMS (N=10) G2: Sham rTMS (N=10) *Medications allowed* No antidepressant medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk	*Inclusion criteria* • Major/Minor Depression (DSM IV), • TRD (1+ failed trial) *Exclusion criteria* NR	*Polarity, %* Major Depression G1: 80 G2: 100 Dysthymia G1: 20 G2: 0 Age, mean yrs G1: 60.5 G2: 60.9 Sex, % females G1: 50 G2: 50 Race, % white G1: 100 G2: 100 *HAM-D* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 22.7 (5.2) G2: 22.7 (7.1)	Change, mean (SD) At week 1 G1: -9 G2: -6.5 1 week follow-up G1: -8.3 G2: -7.2 All time points *P* >0.66; pts with MDD only - *P* = 0.3919 Responders, n (%) G1: 3 (30) G2: 3 (30) *P* = NS Remitters, n G1: 2 G2: 2 *P* = NR	Local pain/local discomfort: 10%/40% vs. 0%/40%; anxiety: 0 vs 10% *Neuropsychological or executive functioning* **30 (endpoint: mean of 3 days after 5 days of txt) Trail Making Test B score Baseline: rTMS: 87.22 Sham: 103.67 Follow-up rTMS: 58.59 Sham: 100.64 **some variation in pts included in two samples but reported as same study by authors. #1564 includes at least 1 participant <50 years old, n=19 Other neuropsychological tests showing no statistical significance in either group: Trail Making Test-A, Stroop Test, WAIS-R digit symbol, Controlled Oral Word Association, Boston naming test,

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham: • Same stimulation, figure 8 coil was above top of skull and handle was placed against head				stentance repitition, Rey Auditory Verbal Learning test, & Judgement of Line Orientation *MMSE* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 28.7 (1.4) G2: 28.6 (1.3) Endpoint score, mean (SD) At Week 1 G1: 29.6(0.7)) G2: 29.3 (0.7) At Follow-up Week 1 G1: 29.6(1.8) G2: 29.2 (0.8) Change, mean (SD) NR 1. *P* >0.41 2. *P* = NA 3. *P* = NR *Attrition* NR *Adherence/ compliance* NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year O'Reardon, 2007[31] *Country, setting* US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported *Funding* Neuronetics *Research Objective* To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral perfrontal cortex is effective and safe inacute treatment of major depression *Quality Rating* Good	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 325 randomized *Duration* 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over aftr 4 weeks if not responding. Interventions G1: Active TMS G2: Sham TMS *Medications Allowed* All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use of hypnotics, anxiolytics for txt emergent insomnia or anxiety *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10	*TRD definition* • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime *Tier 2 Setting(s)* Not clearly reported *Inclusion criteria* • Aged 18—70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed atscreening assessment *Exclusion criteria* • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder • Posttraumatic stress disorder and eating disorders (if present in past year)	*Baseline N* G1: 165 G2: 160 Current episode failures, meanG1: 1.6 G2: 1.6 Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar 100 Age, mean yrs G1: 47.9 G2: 48.7 Sex, % females G1: 55.5% G2: 50.7% Race, % white G1: 94.2% G2: 89.7% *HAM-D 17* Baseline score, mean (SD) G1: 22.6 (3.3) G2: 22.9 (3.5) *MADRS* Baseline n G1: 155 G2: 146	*HAM-D 17* Analyzed n G1: 155 G2: 146 Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5 At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0) Change, mean (SD) At week 2 G1: -5.2 G2: -3.5 At week 6 G1: -5.5 G2: -3.3 *P* = 0.005 Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9) *P* > 0.10 At week 4 G1: 32 (20.6) G2: 17 (11.5)	*Quality of Life* NR *Adverse Events* Serious adverse events G1: 6 G2: 5 Suicidality, % G1: 0.6 G 2: 1.9 • Exacerbation of depression: active TMS = 0.6%, sham TMS = 1.9% • Eye pain: active TMS = 6.1% sham TMS = 1.9%; • GI disorders toothache: active TMS = 7.3%, sham TMS = 0.6%; • Application site discomfort: TMS = 10.9%, sham = 1.3% • Application site pain, %: TMS = 35.8, sham = 3.8 • Facial pain: active TMS = 6.7%, sham TMS = 3.2 • Muscle twitching: TMS = 20.6%, sham = 3.2% • Pain of skin: TMS = 8.5%, TMS = 0.6% *MMSE* NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks rTMS Sham: • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil	• Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head	Baseline score, mean (SD) G1: 32.8 (6.0) G2: 33.9 (5.7) *IDS* Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 42.0 (9.4) G2: 43.4 (9.9) *CGI-S* Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 4.7 (.6) G2: 4.7 (.7)	*P* < 0.05 At week 6 G1: 38 (24.5) G2: 20 (13.7) *P* < 0.05 Remission rate n (%) HAM-D17 < 8 At week 2 G1: 5 (3.2) G2: 3 (2.1) *P* > 0.10 At week 4 G1: 110 (7.1) G2: 9 (6.2) *P* > 0.10 At week 6 G1: 24 (15.5) G2: 13 (8.9) *P* = 0.065 *MADRS* Endpoint score, mean (SD) At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1) At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8) Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1	*Attrition* Overall, % 15 At end of treatment, % G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6% At end of follow-up, % G1: NR G2: NR Withdrawals due to efficacy, % G1: 0.6% G2: 1% Withdrawals due to adverse events, % G1: 5% G2: 4% Other • 325 subjects were randomized • 24 were "nonevaluable" • 301 continued to receive at least 1 treatment, these 301 were included in final analysis • 277 completed study through week 4. *Adherence/ compliance* NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At 6 weeks G1: 6 G2: 3.9 Response rate, % At week 2 G1: 8.4 G2: 6.2 *P* > 0.10 At week 4 G1: 18.1 G2: 11.0 *P* <0.05 At week 6 G1: 23.9 G2: 12.3 *P* <0.01 Remission rate, % Remission defined as total score <10 At week 2 G1: 3.9 G2: 2.1 *P* > 0.10 At week 4 G1: 7.1 G2: 6.2 *P* > 0.10 At week 6 G1: 14.2 G2: 5.5 *P* < 0.05	

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Stern et al., 2007[32] *Country, setting* NR, outpatient setting *Funding* The Milton Fund, NARSAD,Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Cienca *Research Objective* To testhypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in the analysis *N* 45 *Duration* • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse. Primary Outcome: HAM-D at 2 weeksnd and 2 weeks after treatment Interventions G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz toright DLPFC G4: Sham rTMS *Medications allowed* No psychotropic medications were allowed *Parameters* rTMS	*TRD definition* • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode *Tier 2* *Inclusion criteria* • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20 *Exclusion criteria* • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100 % MDD Age, mean yrs G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3 Sex, % females G1: 60 G2: 60 G3: 70 G4: 60 *Right handed, %* 100 *HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10 G4: 15 Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6) Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3) Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3) Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, *P* = 0.001 2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6	*Quality of Life* NR *Adverse Events* 9/45 pts reported severe headaches (pts by group NR); no seizures *Attrition* Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20 Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period. Reported in text as dropped out following week 2.

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600	• Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy		% change, $P = 0.00001$ Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0 At week 2 G1: 5 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$) 1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$) Remitters, n HAM-D ≤ 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%)	*Adherence/ compliance* NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions: 10 days Sham rTMS: • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above *Strategy* Switch			G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 *P* = NS (all times); G2 vs. G4 and G1: vs. G3 *P* = NS (all times)	
Author, Year Wiles et al., 2008[33] *Country, setting* Bristol, UK, 3 general primary care practices, outpatient setting *Funding* NHS *Research Objective* In TRD, can you feasibly compare CBT + CM vs.	*Study design* RCT *Type of analysis* ITT *N* 25 *Duration* 4 months	*TRD definition* • All patients had BDI 15 or more and had complied with an adequate medication *Tier 2* *Inclusion criteria* • 18-65 years; • BDI II score ≥ 15 • have complied with their antidepressant medication	*Subgroups* None *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 100	*BDI* Endpoint score, mean (SD) NR Change, mean (SD) CBT+CM scores decreased by an average of 11.2 points more than CM alone (95%CI -19.3-3.1)	*Quality of Life* Scale NR Baseline n NR Baseline score, mean (SD) NR Endpoint score, mean (SD) NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
CM in primary care (pilot study); primary outcome at 4 months *Quality Rating* Fair	*Interventions* G1: CBT + clinical management G2: Usual Care (clinical management) *Medications allowed* No restrictions *Strategy* Unlimited *Parameters* • Type of therapy: CBT • Method: NR • Number of sessions/week: NR • Total number of sessions: 12-20. • Usual care (no restrictions)	• Met ICD-10 criteria for depression *Exclusion criteria* • Bipolar disorder, psychosis, personality disorder or major alcohol or substance abuse problems; • Those who had been continually depressed for more than 5 years; • Those unable to completestudy questionnaires; • Previous CBT • Those currently receiving other psychotherapy or secondary care for their depression	*BDI* Baseline n G1: 14 G2: 11 Baseline score, mean (SD) G1: 31.1 (8.5) G2: 26.8 (6.8)	Responders, n (%) G1: 8 (57.1) G2: 0 *P* = NR Remitters, n NR	Change, mean (SD) NR There were no differences between groups in QOL at 4mos. (data NR) *Adverse Events* NR *Neuropsychological or executive functioning* No Measures, Results NR Predefined NA - No AE data reported *MMSE* NR *Attrition* Overall, % 8% At end of treatment, % G1: 0 G2: 18.2 At end of followup, % G1: 0 G2: 18.2

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR *Adherence/ compliance* Compliance CBT patients could receive 12-20 sessions. AT 4 mos, median = 9.5 [IQR: 2, 12]. Patients attending <5 sessions (35.7%), patients attending 5-9 sessions (14.3%), patients attending >=10 sessions (50%).

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Bortolomasi et al., 2006[34] *Country, setting* Italy, single center, inpatient vs. outpatient NR *Funding* Not reported *Research Objective* To investigate outcome of depressed patients treated for 1 month with high frequency rTMS onleft frontal lobe at long time periods *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 19 *Duration* Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article **Interventions** G1: rTMS G2: Sham *Medications allowed* Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry) *Strategy* Augmentation Allowed to continue on failed SSRIs (63.2%) and TCAs (26.3%),	*TRD definition* • Drug resistance (not defined) • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations *Exclusion criteria* • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar G1: 83.3 G2: 85.7 Bipolar G1: 16.7 G2: 14.3 Age, mean yrs G1: range 45-56 G2: range 44-53 Overall: 55.6 Sex, % females G1: 58 G2: 57 *Race, % white* NR *Right handed, %* Overall: 100 Groups similar at baseline Yes *Tier* *HAM-D 24* Baseline n G1: 12 G2: 7	*HAM-D 24* Endpoint score, mean (SD) At week 1 G1: 11.33 G2: 18.29 At week 4 G1: 11.42 G2: 19.14 At week 12 NR Change, mean (SD) At week 1 G1: -13.84 G2: NR *P* = NR, significant Group x time at wk 2 and 4, $P < 0.05$ At week 4 G1: -13.75 G2: NR At week 12 NR IG1: rTMS G2: Sham Baseline n G1: 12 G2: 7	*Quality of Life* NR *Adverse Events* No adverse effects were reported in either group, except for mild cephalgia by three patients treated with anti-inflammatory drugs Headache, % 3 patients reported mild headaches after treatment All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep. 3 patients reported mild headaches after treatment *Attrition* *Adherence/ compliance* NR

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	No meds (5.3%) *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil Sham • Stimulation coil was placed perpendicular tothe scalp surface without direct contact. Coil position was fixed for all TMS sessions, and stimulation at this site evoked minimal motor activity		Baseline score, mean (SD) G1: 25.17 G2: NR	Baseline score, mean (SD) G1: 25.42 G2: NR Endpoint score, mean (SD) At week 1 G1: 12.25 G2: 22.43 At week 4 G1: 11.67 G2: 24.57 Change, mean (SD) At week 1 G1: 13.17G2: NR At week 4 G1: 13.75 G2: NR	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year George et al., 1997[35] *Country, setting* USA, outpatient setting *Funding* NARSAD, Ted and Vada Stlanley Foundation *Research Objective* To test hypothesis: daily left prefrontal rTMS has antidepressant effects *Quality Rating* Fair	*Study design* RCT, crossover *Type of analysis* ITT *N* 12 *Duration* 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt Interventions G1: rTMS G2: sham stimulation *Medications Allowed* ADs tapered for 9, 3 partial responders continued their medication *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV criteria for current MDD • right-handed *Exclusion criteria* • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma	*Treatment Failure* Number of previous AD medications Overall: 13.4 *Polarity, %* Unipolar Overall: 91.7 Bipolar II Overall: 8.3 *Age, mean yrs* Overall: 41.8 (12.4) *Sex, % females* Overall: 91.7 *Right handed, %* Overall: 100 *HAM-D 21* Baseline n G1: 12 G2: 12 Baseline score, mean (SD) Overall: 28.5 (4.2)	HAM-D 21 G1: rTMS G2: sham stimulation Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 *P* < 0.03	*Quality of Life* NR *Adverse Events* Headache, % G1: 4/12 G2: NR Suicidality, % G1: 0 G2: Sham: 1/12 Seizures: None Unexpected side effects: None Headaches NR by active v. sham Memory or Attention: None *Attrition* Overall: 0 *Adherence/ compliance* N

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: NR • Pulses per session: • Total number of sessions: 5/wk for a total of 20 per patient Sham: • Same as above but angled at 45 degrees from skull				
Author, Year Harley, 2008[36] *Country, setting* United States, university clinics, outpatient psychiatric *Funding* Kaplan Fellowship Award Grant through Harvard Medical School *Research Objective* To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 24 *Duration* Primary outcome after 16 weeks of active txt Follow-up: 6 months Interventions G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control *Medications Allowed* Patients continued antidepressant therapy *Strategy* Augmentation	*TRD definition* • 1+ failed medications (6+ weeks at "standard effective dose") • Not required or not specified to be in current episode *Tier 2* *Inclusion criteria* • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study.	Baseline N G1: 13 G2: 11 *Treatment Failure* Mean failed trials NR *Polarity, %* MDD *Overall:* 100 *Age, mean yrs* Overall: 41.8 *Sex, % females* Overall: 75 *Race, % white* Overall: 83 *HAM-D 17* Baseline score, mean (SD) G1: 16.15 (4.47)	*HAM-D 17* Analyzed n G1: 10 G2: 9 Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23) Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78 *P* < 0.05 Remitters, n Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) *P* = NR	*Quality of Life* *Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT*) Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24) Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69) Change, mean (SD) G1: -1.3 G2: -0.33 *P* = NS *Social Adjustment Scale-Self-Report (SAS-SR) work subscale* Baseline n G1: 10 G2: 9

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1 Total number of sessions:16 G2: Wait list	*Exclusion criteria* • Borderline personaliy disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder. • Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience.	G2: 18.64 (4.72) *P* = NS *BDI* Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) *P* = NS	*BDI* Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30) Change, mean (SD) G1: -12.80 G2: -1.55 *P* < 0.01	Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95) Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 *P* < 0.05 *Adverse Events* NR *MMSE* NR *Attrition* Overall, %: 21 At end of treatment, % G123 G2:18 At end of follow-up, % G120 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0 Withdrawals due to adverse events, % 0 Other 5 participants (3 groups,

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem prevented second from continuing. *Adherence/ compliance* Compliance Participants completed a weekly check-in form asking about medication compliance overpreceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had forgotten a medication dose between 1 to 4 times in previous month.

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Moller, 2006[37] *Country, setting* Iceland, hospital, inpatient and outpatient *Funding* Government or non-profit organization: Helga Jondottir and Sigurlioi Kristjansson Memorial Fund andLandspitali-University Hopsital of Iceland Research Fund *Research Objective* To evaluate antidepressant efficacy of 5 days of left prefrontal rTMS. *Quality Rating* Fair	*Study design* RCT, crossover *Type of analysis* Cannot tell if ITT, all reported patients included *N* 10 *Duration* Primary endpoint was within one week of completing txt Interventions G1: rTMS G2: Sham *Medications allowed* Pts continued (failed) AD medication and were allowed benzodiazepines *Strategy* Augmentation *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 5	*TRD definition* • TRD not defined • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • Specific inclusion criteria are not reported. • None ofpts received rTMS prior. All met safety criteria. *Exclusion criteria* NR	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 80 Bipolar Overall: 20% *Age, mean yrs* Overall: 54 (14) *Sex, % females* Overall: 60% HAM-D 17 Baseline n G1: 7 G2: 3 Baseline score, median (range) G1: 20 (13 - 37) G2: 16 (7 - 31)	HAM-D 17 G1: rTMS G2: sham rTMS Endpoint score, median (range) G1: 13 (3 - 27) G2: 15 (4 - 25) Change, median-median G1: -7 G2: -1 *P* = 0.075	*Quality of Life* NR *Quality of Life* NR *Adverse Events* Overall, % G1: 30% G2: 0 Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % NR Dizziness, % NR Headache, % G1: 20%; 10% Migraine G2: Insomnia, % NR Post op complications, % NR Somnolence, % NR

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 25 • Pulses per session: 2000 • Total number of sessions: 5 in 5 days Sham • Stimulation was over the occipital cortex (stimulator angled 458 with both wings touching the scullStrategy • Augment or add-on startegy				Suicidality, % NR Additional Comments Only reported on headaches and one migraine. authors do not elaborate on how A.E.s were elicited from pts. Simply, they state, "The magnetic stimulation was well tolerated." *Neuropsychological or executive functioning* Yes; I don't know ifP300 fits in with neuropsychological testing but I've extracted all ofdata from it infollowing column Measures, Results P300 amplitude, n = 9; One pt could not relax and altered outcomes. The median entry P300 amplitude forpatients was 5.7 mV (range 1.0 - 9.5 mV) and latency was 335 ms (range 238 370).P300 amplitude changed from 5.7 mV (range 3.2 - 9.5) to 8.1 mV (range 3.3 - 11.6) after left prefrontal stimulation and after

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					sham stimulation from 7.0 mV (range 1.0 - 13.4) to 8.0 (range 2.2 - 12.3). Comparison of changes inP300 amplitude (left prefrontal-group vs. sham-group) shows a significant difference (n = 9, Z = 2.0, *P* = 0.02). No significant changes were observed inP300 latency.counting performance did not show any difference before and after treatment. Predefined No *MMSE* NR *Other* Only reported on headaches and one migraine. authors do not elaborate on how A.E.s were elicited from pts. Simply, they state, "The magnetic stimulation was well tolerated." Adequate information No

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % NR At end of treatment, % G1: NR G2: At end of follow-up, % G1: NR G2: Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2: *Adherence/ compliance* NR
Author, Year Paykel, 1999[38] Scott, 2000[39] Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219. *Country, setting* UK, outpatient *Funding* Medical Research Council, London, England and a grant	*Study design* RCT *Type of analysis* ITT *N* 158 *Duration* Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68	*TRD definition* • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily	*Treatment Failure* Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar 100% 100% Age, mean yrs G1: 43.2 (11.2) G2: 43.5 (9.8) Sex, % females G1: 53% G2: 46%	HAM-D 17 G1: Clinical Management only G2: CT plus Clinical Management Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2) Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7) Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 20% did not adhere to protocol through to study end or relapse point At end of treatment, % G1: 4 G2: 14

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
fromOxford and Anglia Region *Research Objective* To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintainance treatment with antidepressants. *Quality Rating* Good	wks. Interventions G1: Clinical management Only G2: CT plus Clinical Management *Medications allowed* Continued on current medications with dose adjustments allowed *Strategy* Augmention *Parameters* Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16	dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months. • Failure required to be in the current episode *Tier 2* *Inclusion criteria* • Unipolar depression, • aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression withinlast 18 months but not inlast 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at leastprevious 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose.	*HAM-D 17* Baseline n G1: 78 G2: 80 Baseline score, mean (SD) G1: 12.1(2.7) G2: 12.2 (2.9) P < 0.05 *BDI* Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)	Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 *P* = NS Follow-up at 44 weeks G1: - 3.0 G2: -4.5 Follow-up at 68 weeks G1: -5.0 G2: -4.9 Responders, n NR Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45)) *BDI* Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6), Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3) Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7)	At end of follow-up, % G1: 12 G2: 10 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		Exclusion criteria • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, • any other primary Axis I disorder attime ofindex illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions.		Change, mean (SD) At week 20 G1: -6.24 G2: -8.44 Responders, n NR Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%) Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36) Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93). Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219: Relapse was defined as: (1) meetingDSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms duringfollow-up phase between 2 successive ratings 2 months apart, reaching a score onHAM-D 17 of at least 13 on both occassions and a level of distress or dysfunction for which the withholding of	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				additional active treatment was no longer justified.	
Author, Year West, 1981[40] *Country, setting* UK, Hospital, inpatient *Funding* NR *Research Objective* The therapeutic effect of simulated and real bilateral electric convulsion therapy *Quality Rating* KQ1 - Fair	*Study design* RCT *Type of analysis* Completers or per protocol (PP) *N* 25 (22 analysed) *Duration* 3 weeks *Interventions* G1: ECT G2: Simulated ECT *Medications Allowed* 50 mg amitryptyline *Strategy* Combination *Parameters* The anaesthetic agent was Althesin (alphadolone) and the muscle relaxant suxamethonium. Electric convulsion therapy was administered from a Transycon machine using 40 joules with double-sided unrectified	TRD definition • Referred for ECT *Tier 3* *Inclusion criteria* • Primary depressive illness *Exclusion criteria* • NR	*Subgroups* NR *Baseline n* G1: 13 G2: 12 *Treatment Failure* NR *Polarity, %* NR *Patient Characteristics* *Age, mean yrs* G1: 52.0 G2: 53.3 *Sex, % females* G1: 45 G2: 36 *Race, % white* NR *Not Specified, %* NR *Right handed, %* NR *Groups similar at baseline* Yes	*N Analyzed* G1: 11 G2: 11 *BDI* Yes G1: ECT G2: Simulated ECT Endpoint score, mean (SD) G1: 10.8 (SEM 2.6) G2: 22.2 (3.8) *P* < 0.002 Change, mean (SD) G1: -15.8 G2: -1.9 Responders, n NR Remitters, n NR Other	*Quality of Life* No *Adverse Events* NR *Neuropsychological or executive functioning* No Measures, Results None reported Predefined NA - No AE data reported Adequate information NA - No AE data reported *Attrition* Overall, % 12% At end of treatment, % G1: 15.4 G2: 8.3 At end of followup, % NR

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	waveform and bilateral anterior temporal placement of the electrodes.		*HAM-D 17* Baseline score, mean (SD) *BDI* Baseline score, mean (SD) G1: 26.6 (SEM 2.8) G2: 24.1 (3.5)		Withdrawals due to efficacy, % G1: 7.7 G2: 8.3 Withdrawals due to adverse events, % NR Other *Adherence/ compliance* None reported

Evidence Table 7. KQ1 Non-pharm versus pharm

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Bretlau, 2008[41] *Country, setting* Denmark, setting NR, outpatients *Funding* Commercial source-please list name.supported by Medicon Valley Academy and an unrestricted research grant from H Lundbeck A/S *Research Objective* To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment phase. *Quality Rating* Fair	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 49 *Duration* • 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. • Escitalopram was administered during entire trial at 20mg daily (10 mg daily for first wk of trial). • Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals. *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo	*TRD definition required to be in current episode* Yes *Tier 2* *Setting(s)* Not clearly reported *Inclusion criteria* • Aged 18 - 75 years; • meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); • failed to respond to at least one previous adequate (at least 6 weeks) antidepressant treatment during the current episode; • subjects with heart disorders or diabetes were included if they were in a somatically stable phase *Exclusion criteria* • Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders;	*Subgroups* No sub-group analysis *Treatment Failure* Failed 1 or more, % G1: 100 G2: 100 Failed 2 or more, % NR Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9) Mean failed trials NR *Polarity, %* Unipolar NR Patient Characteristics Age, mean yrs G1: 53.1 G2: 57.8 Sex, % females G1: 68% G2: 57% Race, % white NR Not Specified, % NR	*HAM-D17* G1 G2:Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1),G1: = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2) Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2 Responders, n G1: NR G2: NR	*Quality of Life* NR *Adverse Events* Overall NR Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00 Cardiovascular adverse events, % G1: palpatations: 3wk/ 12 wk mean: 0.23/0.14 G2: 0.30/0.12 Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22 Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06 Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n= 24) G1: rTMS + escitalopram G2: sham TMS + escitalopram G1: rTMS + escitalopram** G2: sham TMS + escitalopram** *Parameters* Location = Left Dorslateral prefrontal cortex Frequency = 8 Hz Intensity = 90% motor threshold Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. Number of sessions = 15 *Strategy* Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment	• potential risk factors for escitalopram such as hypersensitivity to the Intervention, • intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, • pregnancy or insufficient contraception in females of reproductive age; • risk factors for TMS such as history of epilepsy, • metal implants in the head or neck regions, • pacemaker or other electronic implants, • receiving antipsychotics; • having major suicide ideation.	Right handed, % NR *Baseline n* G125 G2:24 Groups similar at baseline Yes *HAM-D17* Baseline score, mean* (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5) *based on rTMS: n = 22 sham: n = 23	Remitters, n G1: NR G2: NR Other • The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favor of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). • HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney *P* = 0.83 (0.22-1.44), *P* = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.78 (0.18 - 1.39), *P* = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.48(-0.12 - 1.07), *P* = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.64 (0.04 - 1.24), *P* = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.47 (	Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (P <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse events inlcude: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				-0.11 - 1.07), *P* = 0.22; • HAM-D6 Awk 2 Effect size (95% CI) and Mann-Whitney *P:* 0.73 (.018 -1.39), *P* = 0.05; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.80 (0.20 - 1.42), *P* = 0.01; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.09 -1.29), *P* = 0.02; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney P:0.50 (-0.10 -1.09), *P* = 0.10; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.0.50 (-0.10 - 1.09), *P* = 0.09; BDI G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0)	12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); *Neuropsychological or executive functioning* No Measures, Results NR Predefined Yes MMSE No NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7), FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9) Change, mean (SD) G1: 12.4 G2: 9.4 Responders, n NR Remitters, n NR Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann-Whitney *P* = 0.73 (0.12 - 1.33), *P* = 0.03; Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.84 (0.24 -1.46), *P* = 0.00; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.64(0.02 - 1.22), *P* = 0.03; FU wk 8 Effect size (95% CI) and	Baseline n NR Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) NR Other *Other* Yes Study utilized the UKU scale as listed before - Other adverse events inlcude: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Mann-Whitney P: 0.65 (0.04 - 1.24), *P* = 0.03; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.46 (-0.12 - 1.06), *P* = 0.12; MADRS NR IDS NR CGI-S NR **CGI-I** NR Instrument Major Depression Inventory (MDI) Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6) Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7)	=0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); Adequate information Yes *Attrition* Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8) Change, mean (SD) G1: 17.4 G2: 14.4 MDI Awk 2 Effect size (95% CI) and Mann-Whitney *P* = 0.36 (-0.23 - 0.94), *P* = 0.18; Awk 3 Effect size (95% CI) and Mann-Whitney P:0.43 (-0.16 - 1.03), *P* = 0.29; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.29 (-0.29 - 0.88), *P* =0.20; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.22 (-0.36 - 0.81), *P* = 0.72; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.23 (-0.36 - 0.81), *P* = 0.43;	in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out. At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0 At end of follow-up, % G1: 21% G2: 4% Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Folkerts et al., 1997[42] *Country, setting* Germany, single center, inpatients *Funding* Not reported *Research Objective* To compare ECT in a controlled, randomized study withserotonin reuptake inhibitor paroxetine in treatment-resistant depression. *Quality Rating* Fair	*Study design* RCT *Type of analysis* per protocol *N* 39 *Duration* Total 6 weeks; Wash-out >= 3days; Phase I ECT - 2wks, Paroxetine - 4 wks; Phase II Paroxetine group - if clinical improvement reduction < 50% treatment switched to ECT, ECT group crossed over to Paroxetine or other antidepressants. Interventions G1: ECT G2: Paroxetine *Medications Allowed* After med wash -out patients were allowed a tranquillizer (diazepam up to 5 mg daily), a sedative (lormetazepam 0.5- 1.0 mg or triazolam 0.25 mg) or a sedative neuroleptic (pipamperon, up to 40 mg daily).	*TRD definition* • 2+ failed treatmentd (8+ weeks) including at least 1 tricyclic, at a dosage of at least 100 imiprimine equivalents • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major depressive episode single and recurrent • Bipolar disorders • HAM-D21 >=22 *Exclusion criteria* • Psychosis • Pronounced suicidal tendency • Severe physical illness • History of substance abuse • previous paroxetine or ECT treatment	*Treatment Failure* Level of tx resistance (Kuhs, 1995) G1: 1.9 (0.7 SD) G2: 2.0 (0.8 SD) Mean failed trials G1: 4.9 G2: 4.3 *Polarity, %* Unipolar G1: 90.5 G2: 83.3 Bipolar G1: 9.5 G2: 16.7 Age, mean yrs G1: 47.6 G2: 52.3 Sex, % females G1: 62 G2: 44 *HAM-D 21* Baseline n G1: 21 G2: 18 Baseline score, mean (SD) G1: 31.1 (4.9) G2: 32.6 (5.4)	*HAM-D 21* Endpoint score, mean (SD) Endof Phase I (ECT: 2-3 wks, Paroxetine: 4 wks) G1: 12.5 (3.9) G2: 23.0 (10.4) Endof Phase II (open trial, 6 weeks) G1: 12.8 (5.1) G2: 15.2 (7.9) Change, mean (SD) End of Phase I G1: -18.6 G2: -9.6 % Reduction in HAM-D, *P* = 0.001 End of Phase II G1: 18.3 G2: 17.4 Responders, n End of Phase I G1: 15 (71.4%) G2: 5 (27.8%) *P*= 0.006	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 0 - all patients continued toscheduled end of treatment At end of treatment, % 0 At end of follow-up, % 0 Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* • All pts continued their respective therapsies through scheduled end of treatment Phase I • 11 of 21 ECT were able to discontinue after 6th ECT session and 10 pts. had 3 additional ECT treatments. • Phase II - of ECT group, 9 received

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters ECT: • % receiving bilateral: 0 • Intensity: 2.5-fold seizure threshold • Number of sessions (range, mean, SD): 3/wk, range 6 to 9, mean 7.2 session Paroxetine • Started at 20 mg/day, within 7 days increased to 40 mg, allowed up to 50 mg, mean dose 44 mg/day for at least 4 weeks *Strategy* Switch				paroxetine and 12 received other antidepressants • Of paroxetine groups, 7 crossed over to ECT • 11 received antidepressants - 7 paroxetine and 4 received other antidepressants • 1 person was excluded from analysis due to failure to increase treatment dosage
Author, Year Moore et al., 1997[43] *Country, setting* Scotland, University clinic, outpatients *Funding* Scottish Office, Home and Health Department *Research Objective* To compare CBT to additional meds in treatment of depression non-responsive to medication duringacute phase of study (results	*Study design* RCT *Type of analysis* Completers confirmed with ITT *N* 13 *Duration* 12 months Interventions G1: Medication G2: Cognitive Therapy	*TRD definition* • Failure to respond to AD medication during 16 wk acute txt phase • Failure required to be in current episode *Tier 2* *Inclusion criteria* • HAM-D > 14 *Exclusion criteria* NA	Baseline N G1: **6** G2: 7 *Treatment Failure* Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar Overall: 100	Analyzed, n G1: 4 G2: 5 *HAM-D 17* Endpoint score, mean (SD) 4 mos G1: 11.0 (2.3) G2: 19.8 (5.6) 8 mos G1: 6.6 (7.3) G2: 17.5 (1.9) 12 mos G1: 5.0 (5.7) G2: 14.3 (4.0)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 31% At end of treatment, % G1: 43 G2: 17 At end of follow-up, % G1: 43 G2: 17

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
of Phase 1 reported elsewhere). *Quality Rating* Fair	Medication Allowed G1: Continued AD assigned in acute phase OR initiated another AD txt G2: Discontinued AD *Strategy* Mixed-between group differences *Parameters* • Medication dose within recognized therapeutic threshold • Psychotherapy • Type of therapy: Cognitive Therapy • Method: NR • Number of sessions/week: min. 3/wk for 4wks and then 2/wk for 4wks and 1/wk for 4wks • Total number of sessions: NR		*Age, mean yrs* Overall: 38 *Sex, % females* Overall: 62 *HAM-D 17* Baseline score, mean (SD) G1: 18.6 (3.3) G2: 18.3 (3.9) *BDI* Baseline score, mean (SD) G1: 30.6 (5.1) G2: 37.8 (5.1)	Completers, group by time, $P < 0.01$ ITT (LOCF), group by time, $P < 0.01$ Change, mean (SD) 4 month G1: -7.6 G2: +1.5 Partial responders, n Defined as HAM-D ≤ 14 G1: 5 G2: 2 $P = 0.17$ Full responders, n Defined as HAM-D ≤ 6 G1: 3 G2: 0 P = NR *BDI* Endpoint score, mean (SD) 4 mos. G1: 22.2 (5.9) G2: 41.5 (5.8) 8 mos. G1: 9.2 (8.3) G2: 34.3 (12.0) 12 mos. G1: 10.8 (12.2) G2: 35.8 (12.6) Group by time, $P = 0.05$ ITT (LOCF), group by time, $P < 0.05$	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Change, mean (SD) At 4 months G1: -8.4 G2: +3.7 Partial responders, n Defined as BDI ≤ 16 G1: 4 G2: 0 *P* < 0.05 Full responders, n Defined as BDI ≤ 9 G1: 3 G2: 0 *P* = NR	
Author, Year Thase et al, 2007[44] *Country, setting* United States, 18 primary care and 23 psychiatric care practice settings, outpatients *Funding* National Institutes of Mental Health *Research Objective* To compare the effectiveness of cognitive therapy and pharmacotherapy as second-step strategies for outpatients with major depressive disorder who had	*Study design* Equipoise-stratified randomization *Type of analysis* ITT *N* 304 *Duration* up to 14 weeks; Interventions G1: Augmentation Cognitive Therapy G2: Augmentation Medication G3: Switch Cognitive Therapy G4: Switch Medication	*TRD definition* • Failed at least one adequate (8 wks or more) treatment in the current episode *Tier 2* *Inclusion criteria* 18 to 75 years; non-psychotic major depressive disorder. HAM-D 17 > 14 *Exclusion criteria* • Remission in initial phase • Bipolar disorder • Schizophrenia, schizo affective disorder, or psychosis not otherwise specified	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD *Age, mean yrs* G1: 40.6 G2: 39.7 G3: 43.4 G4: 41.5 Sex, % females G1: 63.1 G2: 66.7 G3: 61.1 G4: 61.6 Race, % white G1: 80.0 G2: 84.6 G3: 77.8 G4: 73.3	*HAM-D 21* Change, mean (SD) NR Remitters, n (%) HAM-D < 8 G1: 15 (23.1%) G2: 39 (33.3%) *P* = 0.1967 G3: 9 (25.0%) G4: 24 (27.9%) *P* = 0.6881 *QIDS-SR* Mean Score at Endpoint G1: 8.2 (5.1) G2: 8.2 (4.8) *P* = 0.9490 G3: 9.1 (5.4) G4: 9.1 (5.0) *P* = 0.9734	*Quality of Life* Baseline n G1: 65 G2: 117 G3: 36 G4: 86 Baseline score, mean (SD) G1: 41.8 (13.5) G2: 47.7 (14.9), *P* = 0.0202 G3: 43.3 (14.7) G4: 45.5 (13.4), *P* = 0.4634 Endpoint score, mean (SD) NR Change, mean (SD) NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
received inadequate benefit from an initial trial of citalopram. *Quality Rating* Fair	*Medications allowed* See parameters *Strategy* Mixed- between group differences *Parameters* G1: Augmentation to citalopram with Cognitive Therapy: 16 sessions in 12 weeks G2: Augmentation to citalopram with sustained-release bupropion, buspirone G3: Switch from citalopram to cognitive therapy: 16 session in 12 weeks G4: Switch from citalopram to sertraline, sustained-release bupropion, or extended-release venlafaxine	• Anorexia or bulimia • Obsessive compulsive disorder • Clear-cut intolerability to, or lack of effect with, an adequate trial of at least 1 protocol medication or other SSRI in current episode of MDD • Non response to 16 or more sessions of CT or > 7 ECT • General medical condition or medication that contraindicates any level 1 or 2 treatment option • Immediate hospitalization for substance/alcohol detoxification or treatment or psychiatric disorder(s). • Antipsychotic medication or mood stabilizers • Pregnant	*HAM-D 21* Baseline n G1: 65 G2: 117 G3: 36 G4: 86 Baseline score, mean (SD) G1: 17.8 (5.7) G2: 16.0 (6.7) *P* = 0.0962 G3: 16.4 (6.2) G4: 17.7 (6.6) *P = 0.3492* *QIDS-SR* Mean Score at Baseline G1: 11.9 (4.3) G2: 12.0 (4.6) *P* = 0.9495 G3: 11.2 (4.3) G4: 12.1 (4.6) *P* = 0.3282	Mean Score Change G1-29.8 (40.5%) G2: -28.3 (39.6%) *P* = 0.8302 G3: -15.6 (40.7%) G4: -17.2 (46.2%) *P* = 0.9040 Responders, n (%) G1: 23 (35.4%) G2: 33 (28.2%) *P* = 0.2493 G3: 8 (22.2%) G4: 23 (26.7%) *P = 0.8390* Remitters, n (%) QIDS-SR <6 G1: 20 (30.8%) G2: 39 (33.3%) *P* = 0.7803 G3: 11 (30.6%) G4: 23 (26.7%) *P* = 0.9032	*Adverse Events* Maximum side effect frequency *P* = 0.1059 No side effects, n (%) G1: 20 (33.3) G2: 19 (17.3) G3: 2 (100) G4: 14 (18.4) 10–25% of the time, n (%) G1: 16 (26.7) G2: 38 (34.5) G3: 0 (0.0) G4: 25 (32.9) 50–75% of the time, n (%) G1: 13 (21.7) G2: 33 (30.0) G3: 0 (0.0) G4: 18 (23.7) 90–100% of the time, n (%) G1: 11 (18.3) G2: 20 (18.2) G3: 0 (0.0) G4: 19 (25.0) Maximum side effect intensity, *P* = 0.1164 No side effects, n (%) G1: 19 (31.7) G2: 19 (17.3) G3: 2 (100) G4: 13 (17.1) Minimal to mild, n (%) G1: 16 (26.7) G2: 33 (30.0) G3: 0 (0.0) G4: 26 (34.2)

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Moderate to marked, n (%) G1: 21 (35.0) G2: 42 (38.2) G3: 0 (0.0) G4: 27 (35.5) Severe to intolerable, n (%) G1: 4 (6.7) G2: 16 (14.5) G3: 0 (0.0) G4: 10 (13.2) Maximum side effect burden, *P* = 0.1314 No side effects, n (%) G1: 22 (36.7) G2: 24 (21.8) G3: 2 (100) G4: 18 (23.7) Minimal to mild, n (%) G1: 25 (41.7) G2: 47 (42.7) G3: 0 (0.0) G4: 32 (42.1) Moderate to marked, n (%) G1: 11 (18.3) G2: 32 (29.1) G3: 0 (0.0) G4: 22 (28.9) Severe to intolerable, n (%) G1: 2 (3.3) G2: 7 (6.4) G3: 0 (0.0) G4: 4 (5.3)

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Exited because of intolerance, n (%) G1: 6 (9.2) G2: 22 (18.8), *P* = 0.0863 G3: 6 (16.7), G4: 23 (26.7), *P* = 0.2330 At least 1 serious adverse event, n (%) G1: 4 (6.2) G2: 4 (3.4), *P* = 0.4588 G3: 0 (0.0) G4: 2 (2.3), *P* = 1.0000 At least 1 psychiatric serious adverse event, n (%) G1: 4 (6.2) G2: 1 (0.9), *P* = 0.0556 G3: 0 (0.0) G4: 0 (0.0) *Attrition* Overall % NR *Adherence/ compliance* Completed ≥ CBT session G1: 17 (27.4%) G2: NR G3: 10 (34.5%) G4: NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Dannon, 2002[45] *Country, setting* Israel; medical center outpatient program *Funding* National Association for Research in Schizophrenia and Affective Disorders NARSAD) and Stanley Research Foundation *Research Objective* To compare longitudinal outcomes of patients who responded to either rTMS or ECT *Quality Rating* Fair	*Study design* Observational *Type of analysis* Study references Grunhaus 2000 (Refid #368) which is open study of 40 patients - suspect this is continuation of this with additional patients. Of 43 responders initially identified, 2 are excluded *N* 43 *Duration* 3 month and 6 month follow-up; Primary outcome was presence or absence of relapse at 3 or 6 months. Relapse defined as return of depressive symptomatology meeting DSM-IV criteria for MDD with a HAM-D17 score of >= 16 points *Interventions* A - Electroconvulsive Therapy (ECT)B - Repetetive Transcranial Magnetic Stimulation (rTMS)	*TRD definition* • Not required or not specified to be in current episode *Setting(s)* Outpatient *Inclusion criteria* • Responded to treatment with either ECT or rTMS • over age 18 years • DSM-IV diagnosis of MDD with or without psychotic features • no personal or first-degree family history of seizure • no major medical, neurologic, or neurosugical disorder. • Response for inclusion defined as HAM-D17 <= 10 or demonstrating 60% drop in HAM-D and final global assessment scale (GAS) >=60 *Exclusion criteria* NR in this article - but Grunhaus 2000 (Refid #368) reports that patients with additional axis-I diagnoses were excluded from the study	*Subgroups* No sub-group analysis of psychosis although permitted in study *Treatment Failure* Patients referred for ECT because of nonresponse or psychotic MDD Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR Previous treatment, not specified, % G1: NR G2: NR *Polarity, %* Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR Bipolar II G1: NR G2: NR	*HAM-D 17* Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 7.90 (4.54) G2: 7.75 (3.74) Endpoint score, mean (SD) At 3 months G1: 7.71 (5.03) G2: 6.40 (4.91) At 6 months G1: 8.40 (5.60) G2: 7.90 (7.14) Change, mean (SD) At 3 months G1: -0.01 G2: 1.35 At 6 months G1: -0.5 G2: -0.15 Responders, n NR Remitters, n NR Relapse (HAM-D ≥ 16) At 3 months G1: 2 G2: 1	*Quality of Life* Global Assessment of Functioning (GAF), or GAS Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 71.81 (10.39) G2: 72.50 (9.39) Endpoint score, mean (SD) At 3 months G1: 75.52 (13.81) G2: 79.75 (12.92) At 6 months G1: 72.8 (11.94) G2: 77.75 (17.13) Change, mean (SD) At 3 months G1: -3.71 G2: -7.25 At 6 months G1: -0.99 G2: -5.25 Other 3 mos *P* = NS, CI -12.69, 4.23; 6 mos *P* = NS, CI -14.40, 4.50 *Adverse Events* NR

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	G1: ECT G2: rTMS Antidepressants prescried at end of ECT and rTMS for all patients *Parameters* rTMS: Location = Left Dorsolateral Prefrontal Cortex Frequency = 10Hz Intensity = 90% MT Per Session = 6 sec trains with 30 sec interval in between at 20 times. Number of sessions = daily for 20 days ECT Methods: Location: Initially unilateral; switched to bilateral txt after 6th txt if HRSD had not decreased by >= 30% Threshold = 2.5 times threshold energy to maintain a seizure length of >= 25 sec. Number of sessions = NR *Strategy* There is no description of whether participats were taking medications prior to treatment with ECT or rTMS. Co-medications were not		Age, mean yrs G1: 57.43 G2: 56.85 Sex, % females G1: 70% Note: there might be a typo in table in reporting gender ratio, percentage reported here is based on numbers in"rTMS" column in paper because they add up to correct n for "ECT column." G2: 66.7% Race, % white G1: NR G2: NR Right handed, % G1: NR G2: NR Groups similar at baseline No- what are differences All *P* values were reported as non-significant for baseline characteristics, however following characteristics showed some variation between groups: Duration of episode (months) (mean +/- SD), ECT grou*P* = 6.71 +/- 7.56, rTMS gr	At 6 months G1: 2 G2: 3 Combined G1: 4 G2: 4 Other HAM-D17 3 mos = *P* = NS, CI -1.83, 4.46; 6 mos = *P* = NS, CI -3.61, 4.61 ECT vs. rTMS *BDI* NR *MADRS* NR *IDS* NR *CGI-S* NR *CGI-I* No NR Baseline n NR Endpoint score, mean (SD) NR	*Neuropsychological or executive functioning* No Measures, Results NR Predefined NA - No AE data reported *MMSE* NR *Attrition* Overall, % 4.6% At end of treatment, % NR At end of follow-up, % G1: 0 G2: 9 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: NR G2: NR Other 43 people agreed to be part of study, two were dropped before final analysis, no explanation is given, and they are

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	allowed during period when ECT or rTMS was given with exception of lorazepam. Antidepressants		*Tier* Tier 3 only mention of whetherparticipants failed any previous treatments is in Grunhaus (#368).	Achieving 1 or 2 score, %(SD) NR Other NR *Other*	not included in final analysis. The Michigan Adequacy of Treatments (MATS) was also included in this study. MATS for ECT was 3 mos FU 1.92 (1.04 SD), 6 mos FU 1.82 (0.98 SD); rTMS 3 mos FU 2.28 (1.07 SD), 6mos 2.44 (1.03 SD). CI for 3 mos FU ECT vs. rTMS is -1.14 - 0.43, *P* = N *Adherence/ compliance* NR

Evidence Table 8. KQ1 pharm versus pharm: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Berman, 2007[46] Berman *Country, setting* United States Multicenter, outpatient setting *Funding* Bristol-Myers Squibb Co Otsuka Pharmaceutical Co *Research Objective* To compare the efficacy, safety, and tolerability of aripiprazole vs. placebo as adjunctive treatment to standard antidepressant therapy in the treatment of an MDE in pts who have shown an incomplete response to ADT *Quality Rating* Fair	*Study design* RCT *Type of analysis* Modified ITT (m-ITT) *N* Prospective tx phase: 781 Double-blind tx phase: 366 (4 did not receive medication and were not included) *Duration* Prospective tx phase: 8 wks Double-blind tx phase: 6 wks Primary outcome MADRS total score at endpoint 8 wks. Additional efficacy measures collected weekly. *Interventions* Antidepressant + (Augmenter vs. Placebo) G1: Placebo augmentation G2: aripiprazole augmentation augmentation Attrition based on mITT NA	*TRD definition* • Failed two or more adequate treatment failures (> 6 wk duration). • OR Inadequate response to at least 1 and no more than 3 adequate AD trials (> 6 wks duration at adequate dose) prior to inclusion. • Pts also had to establish inadequate antidepressant response in prospective treatment phase (8 wk duration) • Required a failure current episode *Tier 1* *Inclusion criteria* • Outpatients 18-65 years; could understand, comply, and provide written consent. • MDE lasting ≥ 8 wks prior to inclusion without adequat response • At least 1, no more than 3 adequate AD trials without adequate response.	*Subgroups* NA - KQ1 Drug Study *Baseline n* G1: 178 G2: 184 *Treatment Failure* Failed 1 or more, % G1: 100.0 G2: 100.0 Failed 2 or more, % G1: 100 G2: 100 Current episode failures, mean Failed 2+ in current episode G1: 33.6 G2: 33.5 Mean failed trials NR *Polarity, %* Unipolar G1: 100 G2: 100 Bipolar I G1: 0 G2: 0	*HAM-D (Insert #)* NR *BDI* NR *MADRS* Yes G1: Placebo Augmenter G2: aripiprazole Augmenter Baseline n mITT Population G1: 172 G2: 181 Baseline score, mean (SD) G1: 25.9 (6.5) G2: 26.0 (6.1) Endpoint score, mean (SD) Calculated endpoint score G1: 20.1 (NR) G2: 17.2 (NR) Change, mean (SD) Endpoint (6wk) G1: -5.8 G2: -8.8 G1: vs. G2, *P* < 0.001	*Quality of Life* NR *Adverse Events* NA *Neuropsychological or executive functioning* NA Measures, Results NA Predefined NA MMSE NR *Other* NA *Attrition* Overall, % Double-blind tx phase: 10% (mITT); 11.6% (ITT) At end of treatment, % G1: 9.1% G2: 12.1% At end of followup, % NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Medications Allowed Augmentation - Distribution of Ad at randomization: Escitalopram 29.6%; fluoxetine 14.2%, paroxetine 8.9%, sertraline 19.8%, venlafaxine 27.4% *Strategy* Other, please explain: Prospective tx phase - switch strategy; Double-blind treatement phase - augmentation strategy *Parameters* G1: Placebo G2: 5-20 mg/day	• HAM-D17 Total score ≥ 18; For continuation into double-blind tx phase HAM-D17 total score representing <50% reduction in symptoms during prospective tx phase, HAM-D17 total score ≥14; CGI-I score of ≥ 3 • Most psychotropic meds, including benzodiazepines and other hypnotics discontinued. *Exclusion criteria* • Current Axis I diagnosis of delirium, dementia, amnestic, or other cognitive disorder, panic disorder, or post traumatic stress disorder. • Current Axix II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. • Pts experiencing hallucinations, delusions, or any psychotic symptomatology in the current episode	Bipolar II G1: 0 G2: 0 *Patient Characteristics* *Age, mean yrs* G1: 44.2 G2: 46.5 *Sex, % females* G1: 64.2 G2: 61.5 *Race, % white* G1: 92.6 G2: 87.4 *Not Specified, %* G1: 0 G2: 0 *Right handed, %* NR *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) NR *BDI* Baseline score, mean (SD)	Week 2 G1: -3.4 G2: -6.3 G1: vs. G2, *P* <0.001 Responders, n Endpoint (6wk) G1: 23.8% (n = 41) G2: 33.7% (n = 61) G1: vs. G2, *P* = 0.027 Week 5 G1: 20.3% G2: 33.1% G1: vs. G2, *P* < 0.01 Week 4 G1: 15.7% G2: 30.4% G1: vs. G2, *P* < 0.001 Week 3 G1: 15.7% G2: 25.4% G1: vs. G2, *P* < 0.05 Week 2 G1: 8.1% G2: 16.6% G1: vs. G2, *P* < 0.05	Withdrawals due to efficacy, % G1: 1.1% G2: 1.1% Withdrawals due to adverse events, % G1: 2.3% G2: 3.3% Other *Adherence/ compliance* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		• Significant substance use disorder within 12 months. • Allergy, hypersensitivity, or previous unresponsiveness to aripiprazole. • Participation in a clinical trial w/ aripiprazole or any other investigational product within past month • History of thyroid pathology, neuroleptic malignant syndrome, serotonin syndrome. • History of seizure disorder • Postive screen for drugs of abuse • Receipt of adjunctive antipsychotic + antidepressant for ≥ 3 wks during current episode • Receipt of ECT for current episode • Inadequate response to previous ECT in any episode	NR	Week 1 G1: 1.8% G2: 6.2% G1: vs. G2, *P* = 0.025 Remitters, n Endpoint G1: 15.7% (n = 27) G2: 26.0% (n = 47) G1: vs. G2, *P* = 0.011 Week 5 G1: 14.0% G2: 26.0% G1: vs. G2, *P* < 0.01 Week 4 G1: 11.0% G2: 22.7% G1: vs. G2, *P* < 0.01 Week 3 G1: 8.7% G2: 18.8% G1: vs. G2, *P* = 0.006 Week 2 G1: 5.8 G2: 10.5 G1: vs. G2, *P* = NS	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 1 G1: 1.8 G2: 3.4 G1: vs. G2, *P* = NS Other Response defined as ≥ 50% reduction in MADRS total score. Remission defined as response plus an absolute MADRS total score of ≤ 10. *IDS* G1: Placebo G2: aripiprazole[Q60] Baseline n ITT Population G1: 172 G2: 181 Baseline score, mean (SE) G1: 34.0 (1.1) G2: 34.4 (1.0) Endpoint score, mean (SE) Calculated G1: 28.8 (NR) G2: 27.4 (NR) Change, mean (SE) G1: -5.2 (0.8) G2: -7.0 (0.8)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				P = 0.076 **Text reports "While differences on the IDS-SR were significant at weeks 2, 3, 4, and 5, significance was not shown at endpoint" Data not shown. Responders, n NR Remitters, n NR CGI-S Baseline n mITT Population G1: 172 G2: 181 Baseline score, mean (SE) G1: 4.11 (0.05) G2: 4.08 (0.04) Endpoint score, mean (SE) Calculated G1:3.47 (NR) G2: 3.05 (NR) Change, mean (SE) Endpoint G1: -0.64 (0.08) G2: -1.03 (0.08) G1: vs. G2, *P* < 0.001	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				CGI-I Baseline n G1: 172 G2: 181 Endpoint score, mean (SE) G1: 2.81 (0.09) G2: 2.49 (0.08) G1: vs. G2, *P* = 0.003 Achieving 1 or 2 score, %(SD) Endpoint: G1: 37.2 G2: 53.0 G1: vs. G2, *P* = 0.002 Week 5: G1: 32.6 G2: 51.4 G1: vs. G2, *P* < 0.001 Week 4: G1: 31.4 G2: 52.5 G1: vs. G2, *P* < 0.001 Week 3: G1: 28.5 G2: 45.3 G1: vs. G2, *P* <0.001	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 2: G1: 22.7 G2: 35.0 G1: vs. G2, *P* = 0.010 Week 1: G1: 12.2 G2: 18.3 G1: vs. G2, *P* = 0.123 *Other* NR	
Author, Year Berman, 2009[47] *Country, setting* United States Multicenter *Funding* Bristol-Myers Squibb Co Otsuka Pharmaceutical Co *Research Objective* To evaluate the efficacy and safety of adjunctive aripiprazole vs. antidepressant monotherapy in pts with MDD and independently replicate the positive findings of two similar trials.	*Study design* RCT *Type of analysis* mITT *N* Prospective tx phase: 827 Double-blind tx phase: 349 *Duration* Prospective tx phase: 8 wks Double-blind tx phase: 6 wks Primary outcome MADRS total score at endpoint 8 wks. *Interventions* Antidepressant + Augmenter vs. Placebo	*TRD definition* Required to be in current episode Yes *Tier 1* *Setting(s)* Not Clearly reported *Inclusion criteria* • Patients 18-65 yrs of age • DSM-IV criteria for MDE lasting ≥ 8 wks. • Inadequate response to prior antidepressant to 1-3 antidepressant trials of ≥ 6wk duration. • Inclusion into double-blin tx phase required meeting criteria for inadequate response score from baseline to	*Subgroups* NA - KQ1 Drug Study *Baseline n* G1: 172 G2: 177 *Treatment Failure* Failed 1 or more, % G1: 68.0 G2: 71.8 Failed 2 or more, % G1: 100.0 G2: 100.0 Current episode failures, mean Failed 2+ in current episode (%) G1: 29.1 G2: 26.6	*N analyzed* G1: 169 G2: 174 *HAM-D (Insert #)* Yes HAM-D17 G1: Placebo augmentation G2: aripiprazole augmentation Endpoint score, mean (SD) Calculated: G1: 14.9 (NR) G2: 12.2 (NR) Change, mean (SD) G1: -5.1 (0.6 SE) G2: -7.6 (0.6 SE) G1: vs. G2, *P* <0.001	*Quality of Life* NR *Adverse Events* NA *Neuropsychological or executive functioning* NA Measures, Results NA Predefined NA MMSE NR *Other* NA Adequate information NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Quality Rating Fair	Augmenter G1: Placebo augmentation G2: aripiprazole augmentation G1: Placebo augmentation G2: aripiprazole augmentation NA *Medications Allowed* All pts taking an antidepressant at randomization - Distribution - Aripiprazole Group: Escitalopram: 33.9%; fluoxetine: 17.5%; paroxetine: 7.9%; Sertraline 11.9%; Venlafaxine ER: 28.8% Placebo Group: excitalopram: 30.2%; fluoxetine: 14.5%; paroxetine: 11.6%; sertraline: 17.4%; venlafaxine ER: 26.2% *Strategy* Augment *Parameters* G1: Plabebo augmentation G2: 2-20 mg/day	end of prospective treatment phase, a HAM-D 17 total score of ≥ 14, and a CGI_I score ≥ 3 at wks 6 and 8. • Stable doses of hypnotics for insomnia, including benzodiazepines and other sleep aider discontinued ≥1 wk prior to prospective tx phase. • All psychotropics prohibited. • Txt of extrapyramidal symptoms permitted during study. *Exclusion criteria* • Current Axis I diagnosis of delirium, dementia, amnestic, or other cognitive disorder, panic disorder, or post traumatic stress disorder. • Current Axix II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. • Pts experiencing hallucinations, delusions, or any	Mean failed trials NR *Polarity, %* Unipolar G1: 100 G2: 100 Bipolar I G1: 0 G2: 0 Bipolar II G1: 0 G2: 0 *Patient Characteristics* *Age, mean yrs* G1: 45.6 G2: 45.1 *Sex, % females* G1: 68.0 G2: 78.0 *Race, % white* G1: 86.6 G2: 87.6 *Not Specified, %* NR *Right handed, %* NR *Groups similar at baseline* No -	Responders, n NR Remitters, n NR BDI NR MADRS Yes G1: Placebo Augmenter G2: aripiprazole Augmenter Baseline n mITT (n analyzed) G1: 169 G2: 174 Baseline score, mean (SD) G1: 27.1 (5.8) G2: 26.6 (5.8) Endpoint score, mean (SD) Calculated: G1: 20.7 (NR) G2: 16.5 (NR) Change, mean (SD) G1: -6.4 (NR) G2: -10.1 (NR) G1: vs. G2, *P* <0.001 Treatment difference: -3.7 (95%CI -5.4, -2.0)	*Attrition* Overall, % Double-blind tx phase: 15.2% At end of treatment, % G1: 13.4 G2: 16.9 At end of followup, % NA Withdrawals due to efficacy, % G1: 1.7 G2: 1.1 Withdrawals due to adverse events, % G1: 1.7 G2: 6.2 Other *Adherence/ compliance*

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		psychotic symptomatology in the current episode • Significant substance use disorder within 12 months. • Allergy, hypersensitivity, or previous unresponsiveness to aripiprazole. • Participation in a clinical trial w/ aripiprazole or any other investigational producet within past month • History of thyroid pathology, neuroleptic malignant syndrome, serotonin syndrome. • History of seizure disorder. • Postive screen for drugs of abuse. • Receipt of adjunctive antipsychotic + antidepressant for ≥ 3 wks during current episode. • Receipt of ECT for current episode • Inadequate response to previous ECT in any episode	Aripiprazole group 138 females (78%) vs. Placebo 117 females (68%) *HAM-D 17* Baseline score, mean (SE) G1: 20.0 (0.4) G2: 19.8 (0.4) *BDI* Baseline score, mean (SD) NR	Responders, n G1: 26.6% (n = 45) G2: 46.6% (n = 81) G1: vs. G2, *P* < 0.001 Remitters, n G1: 18.9% (n = 32) G2: 36.8% (n = 64) G1: vs. G2, *P* <0.001 Alternate definitions MADRS total score ≤ 12 G1: 27.2% G2: 43.7% G1: vs. G2, *P* < 0.001 MADRS total score ≤ 8 G1: 14.2% G2: 27.6% G1: vs. G2, *P* < 0.01 Other Response defined as ≥ 50% reduction in MADRS total score. Remission defined as ≤ 10 and ≥ 50% reduction in MADRS total score. Alternate Remission Definitions: MADRS total score ≤ 12; MADRS ≤ 8 IDS Yes	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G1: Placebo Augmenter G2: aripiprazole Augmenter[Q60] Baseline n G1: 169 G2: 174 Baseline score, mean (SE) G1: 33.0 (1.1) G2: 32.7 (1.1) Endpoint score, mean (SE) Calculated: G1: 27.6 (NR) G2: 25.8 (NR) Change, mean (SE) G1: -5.4 (1.1) G2: -6.9 (0.9) G1: vs. G2, *P* = 0.12 Responders, n NR Remitters, n NR CGI-S Yes G1: Placebo Augmenter G2: aripiprazole Augmenter	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Baseline n G1: 169 G2: 174 Baseline score, mean (SE) G1: 4.2 (0.1) G2: 4.1 (0.1) Endpoint score, mean (SE) Calculated: G1: 3.5 (NR) G2: 3.0 (NR) Change, mean (SE) G1: -0.7 (0.1) G2: -1.1 (0.1) G1: vs. G2, *P* <0.001 CGI-I Yes G1: Placebo Augmenter G2: aripiprazole Augmenter Baseline n G1: 169 G2: 174 Endpoint score, mean (SE) G1: 2.8 (0.1) G2: 2.4 (0.1) G1: vs. G2, *P* = 0.001	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Achieving 1 or 2 score, %(SD) G1: NR G2: NR *Other* Validated measure Yes Instrument QIDS-SR Intervention G1: Placebo Augmenter G2: aripiprazole Augmenter Baseline n G1: 169 G2: 174 Baseline score, mean (SE) G1: 12.8 (0.4) G2: 13.0 (0.4) Endpoint score, mean (SE) Calculated: G1: 10.7 (NR) G2: 10.2 (NR) Change, mean (SE) G1: -2.1 (0.3) G2: -2.8 (0.3) G1: vs. G2, P = 0.08	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Corya et al., 2006[48] *Country, setting* Multinational, 16 countries, 90 centers *Funding* Eli Lilly *Research Objective:* Olanzapine/fluoxetine combination (OFC) was examined in comparison with olanzapine, fluoxetine, and venlafaxine in a TRD population. *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N: 483* *Duration:* 12 weeks *Primary outcome:* Change in MADRS at 12 weeks *Interventions* G1: Olanzapine/fluoxetine G2: Olanzapine G3: Fluoxetine G4:Venlafaxine G5: Low-dose Olanzapine/fluoxetine *Parameters* G1: Olanzapine/fluoxetine: Combined 4 groups G2: Olanzapine: 6 or 12 mg/d G3: Fluoxetine: 25 or 50 mg/d G4:Venlafaxine: 75-375 mg/d G5: Low-dose Olanzapine/fluoxetine: 1mg/d olanzapine, 5 mg fluoxetine	*TRD definition:* "…documented history of a failure to achieve a satisfactory response to a selective serotonin reuptake inhibitor (SSRI) antidepressant after at least 6 weeks of therapy at a therapeutic dose" and subsequently showing less than 30% improvement after 7 weeks of venlafaxine treatment; Failure within current episode Remission defined as MADRS ≤ 8 at two consecutive visits *Setting(s)* *Inclusion criteria:* 18 years ; CGI-S 4 or greater, MDD w/o psychotic features; documented history of TRD *Exclusion criteria:* schizophrenia, schizoaffective disorder; other psychotic disorders, bipolar I or II disorder, PTSD, MDD w/ seasonal pattern, or dissociative disorders; pregnant or nursing; concomitant	*Subgroups; none* *Treatment Failure* Failed 2 or more, 100% Current episode failures, mean NR Mean failed trials *Polarity, %* Unipolar 100% *Age, mean yrs* Overall: 45.7 *Sex, % females* Overall: 72.5% *Race, % white* Overall: 89.9 *Right handed, %* NR and NA Groups similar at baseline Group baseline characteristics NR just overall *Tier 1*	*HAM-D NR* *MADRS* Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59 Baseline score, mean (SD) 30.0 (6.8) for overall sample (moderate-to-severe range) Endpoint score, mean (SD) NR Change, mean (SD) G1: -14.06 (0.59) G2: -7.71 (1.17) G3: -11.70 (1.14) G4: -13.73 (1.16) G5: -11.97 (1.13) G1: (OFC) vs. G2 (Ola), *P* < 0.001. all others NS Responders, n (%) G1: 100 (43.3) G2: 15 (25.4) G3: 19 (33.9) G4: 29 (50.0) G5: 20 (36.4) G! (OFC) vs. G2 (Ola), *P* = 0.017. all others NS	*Quality of Life: NA* *Adverse Events: NA* *Neuropsychological or executive functioning: NA* *MMSE:NA* *Attrition: NA* *Adherence/ compliance: NA*

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Switch	medications with primary CNS activity w/ exception of benzodiazepines up to an equivalent of 4mg of lorazepam per day		Remitters (MADRS ≤ 8 for any two consecutive visits), n (%) G1: 69 (29.9) G2: 8 (13.8) G3: 10 (17.9) G4: 13 (22.4) G5: 11 (20.0) G1: (OFC) vs. G2 (Ola), *P* = 0.013. all others NS CGI-S Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59 Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: -1.51 (0.07) G2: - 0.91 (0.15) G3: -1.26 (0.15) G4: -1.49 (0.14) G5: -1.23 (0.14) G1: (OFC) vs. G2 (Ola), *P* < 0.001. all others NS	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				BPRS Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59 Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: -6.01 (0.40) G2: ---3.16 (1.04) G3: -4.82 (0.88) G4: -4.76 (0.98) G5: -6.33 (0.87) G1: (OFC) vs. G2 (Ola), *P* = 0.008. all others NS	
Author, Year Fang et al., 2010[49] *Country, setting* China - multicenter (8), both inpatient and outpatients included *Funding* B10th Five-year Plan[of National Key Technologies R&D Program grants 2004BA720A21-02 (Ministry of Science and	*Study design* RCT *Type of analysis* ITT *N* 150 *Duration* 8 weeks *Interventions* G1: Venlafaxine-XR 225 mg/d (n = 50)	*TRD definition* • Failed two or more adequate (12 weeks or more each) treatments from different classes in the current depressive episode. • Required to be in current episode *Tier 1* *Inclusion criteria* • Ages of 18 and 65 years with a diagnosis	*Subgroups* No *Baseline n* G1: 50 G2: 55 G3: 45 *Treatment Failure* Failed 1 or more, % 100 Failed 2 or more, % 100	*HAM-D (17)* Endpoint score, mean (SD) G1: G2: G3: Change, mean (SD) NR Responders, n G1: 32 G2: 32 G3: 30	*Quality of Life* NR *Adverse Events* NA *Neuropsychological or executive functioning* NA *MMSE* NR *Other* NR

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Technology of China) and the Climbing Mountain Action Plan[Program grants 064119533 (Science and Technology Commission of Shanghai Municipality) and partly supported by National High-tech R&D Program (863 Program) grants 2006AA02Z430 (Ministry of Science and Technology of China). *Research Objective* Compare the efficacy and tolerability of antidepressants switch with extended-release venlafaxine (venlafaxine-XR), mirtazapine, and paroxetine in Chinese patients with MDD who had 2 consecutive unsuccessful antidepressant trials *Quality Rating* Fair	G2: Mirtazapine45 mg/d (n = 55) G3: Paroxetine20 mg/d (n = 45) *Medications Allowed* All patients switched to a new pharmacotherapy *Strategy* Switch strategy *Parameters* venlafaxine-XR 225 mg/d (Effexor; Wyeth, China); mirtazapine, 45 mg/d (Remeron; Organon, China); and paroxetine, 20 mg/d (Paxil; GlaxoSmithKline)	of MDD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and from inpatient and outpatient services • Meet stage 2 TRD criteria described by Thase and Rush. 9 Stage 2 TRD in this study was retrospectively and/or prospectively. *Exclusion criteria* • Lifetime diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or other psychotic disorders • Imminent risk for suicide or homicide judged by a research psychiatrist • Any medical contraindication to antidepressants or other psychotropic medication • Unstable general medical condition or a condition that required combination treatment of an antidepressant and any other psychotropic medication	Current episode failures, mean NR Mean failed trials NR *Polarity, %* Unipolar 100 Bipolar I 0 Bipolar II 0 *Patient Characteristics* *Age, mean yrs* Overall 40.5 years *Sex, % females* Overall 54% *Race, % white* NR *Not Specified, %* 0 *Right handed, %* NR *Groups similar at baseline* Yes	Remitters, n G1: 21 G2: 20 G3: 21 Other There were no significant differences in the remission rates among the 3 groups (W2 = 1.097, df = 2, *P* = 0.578), Response Rates *P* = 0.664. There were also no significant differences among the groups in the cumulative proportion of remission rates at each postbaseline visit (log rank, W2 = 0.4974, df = 2, *P* = 0.7798). *BDI* NR *MADRS* NR *IDS* NR *CGI-S* NR CGI-I Yes	*Attrition* Overall, % 0.18 At end of treatment, % G1: 18.0% G2: 18.2% G3: 17.8% At end of followup, % NA Withdrawals due to efficacy, % G1: 2 G2: 6 G3: 6 Withdrawals due to adverse events, % G1: 0 G2: 0 G3: 2 *Adherence/ compliance* NR

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		(including typical/atypical antipsychotic agents, mood stabilizers, anticonvulsants, and stimulants) • Modified electroconvulsive therapy within 1 month of study screening • Pregnant, planning to become pregnant, or breast-feeding	*HAM-D 17* Baseline score, mean (SD) Overall 24.6 (5.8) *BDI* Baseline score, mean (SD)	G1: Venlafaxine G2: Mirtazapine G3: Paroxetine Achieving 1 or 2 score, %(SD) CGI = 1 G1: 48.0 G2: 29.1 G3: 40.0 Other *P* = 0.136 *Other* NR	
Author, Year: Fava et al., 2006[50] *Country, setting:* USA, Multicenter 18 primary and 23 psychiatric centers *Funding:* NIMH *Research Objective:* Compared the efficacy of switching to mirtazapine vs. nortriptyline following two prospective, consecutive, unsuccessful medication treatments for non-psychotic MDD	*Study design* RCT *Type of analysis* ITT N: 235 *Duration:* 12-14 weeks Interventions G1: Mirtazapine G2: Nortriptyline *Parameters* G1: Mirtazapine: Up to 60mg/day G2: Nortriptyline: Up to 200mg/day *Strategy:* Switch	*TRD definition:* 2 or more in current episode. Remission defined as HAM-D17 ≤ 7 *Tier 1* *Setting(s)* Outpatient; Psychiatric and Primary Care Practices Inclusion criteria: • Outpatients with a primary diagnosis of non-psychotic MDD *Exclusion criteria:* • Psychotic disorders, OCD	*Subgroups-* None *Treatment Failure* Failed 1 or more, 100% Failed 2 or more, 100% Current episode failures, mean Overall: 2 Failed trials, mean Overall: 2 Previous treatment, not specified, 0% *Polarity, %* Unipolar	*HAM-D 17* G1 G2: G1 G2:Endpoint score, mean (SD) G1: NR G2: NR Change, mean (SD) G1: NR G2: NR Average percentage improvement G1: NR G2: NR Responders, n G1: NR G2: NR	*Quality of Life:* NA *Adverse Events:* NA *Neuropsychological or executive functioning:* NA *MMSE:* NA *Attrition:* NA *Adherence/ compliance:* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Quality Rating: Good	*Diagnosis:* 100% MDD	• Eating disorders • General medical conditions contraindicating the use of protocol medications • Substance dependence (only if it required inpatient detoxification) • Pregnant • Breastfeeding. Stable psychotropic medications allowed. Stimulant, anticonvulsant, antipsychotic mood stabilizing, nonprotocol antidepressants and potential antidepressant augmenting agents (e.g. busiprone) were not allowed. Anxiolytics (except alprazolam) and sedative hypnotics (including trazodone for sleep)	G1: 100 G2: 100 Bipolar I G1: 0 G2: 0 Bipolar II G1: 0 G2: 0 *Age, mean yrs* G1: 44.8 G2: 45.1 *Sex, % females* G1: 42.1 G2: 51.2 *Race, % white* G1: 80.7 G2: 76.0 *Right handed, %* NR *HAM-D 17* Baseline n G1: 114 G2: 121 Baseline score, mean (SD) G1: 19.8 (7.0) G2: 18.6 (5.9) Groups similar at baseline: Yes. More in mirtazapine 24.6% had attempted suicide vs. nortriptyline 12.4%, but this difference was controlled for in the analyses.	Remitters, n G1: 14 (12.3%) G2: 24 (19.8%) G1: vs. G2, P=0.27 *QIDS-SR* Baseline n G1: 114 G2: 121 Baseline score, mean (SD) G1: 14.1 (5.0) G2: 14.0 (4.7) Endpoint score, mean (SD) G1: 12.6 (5.4) G2: 12.2 (5.9) Change, mean (SD): NR Average percentage improvement G1: -7.1% (35.2) G2: -10.9 (36.5) G1: vs. G2, p=0.48 Responders (50% reduction), n G1: 15 (13.4%) G2: 20 (16.5%) G1: vs. G2, p=0.57 Remitters (< 5), n G1: 9 (8.0%) G2: 15 (12.4%)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Mazeh et al., 2007[51] *Country, setting* Israel, inpatient, single center *Funding:* NR *Research Objective:* compare the efficacy and tolerability of venlafaxine vs. paroxetine in elderly patients suffering from resistant major depression *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N= 30* *Duration:* 6 weeks Interventions G1: Paroxetine (mean 26 mg/day) G2: Venlafaxine (165 mg/day) *Parameters* G1: Paroxetine: 10-60mg/d(mean 26 mg/day) G2: Venlafaxine 75-300mg/d (mean 165 mg/day) *Strategy –* Switch	*TRD definition:* "…they did not respond to two adequate pharmacological treatments for depression during this depressive episode." Remission defined as HAM-D21 ≤ 7 *Setting(s);* Mental Health Center *Inclusion criteria*; MDD; 18 or more on Ham-D21;inpatient; ≥ 65 years old *Exclusion criteria;* Dementia; exposure to study drugs *Diagnosis* 100% MDD	*Subgroups* *Treatment Failure* NR *Polarity, %* Unipolar NR *Age, mean yrs* G1: 77.7 G2: 74.1 *Sex, % females* G1: 60 G2: 53 *Race, % white* NR *Right handed, %* NR *Groups similar at baseline* Yes *Tier* Tier 1	*HAM-D 21* Baseline n G1: 15 G2: 15 Baseline score, mean (SD) G1: 30.1 (7.9) G2: 26.3 (5.9) Endpoint score, mean (SD) G1: NR G2: NR Change, mean (SD) G1: -12.5 G2: -19.1 *P*<0.0003 Average percentage improvement G1: NR G2: NR Responders, n (%) G1: 8 (53) G2: 12 (80) *P* = NR Remitters, n (%) G1: 5 (33) G2: 9 (60) *P* = NR Data primarily reported in figures Other	*Quality of Life:* NA *Adverse Events:* NA *Neuropsychological or executive functioning:* NA *MMSE:* NA *Attrition:* NA *Adherence/ compliance:* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				CGI-S Baseline n G1: 15 G2: 15 Baseline score, mean (SD) G1: 5.7 (0.9) G2: 5.5 (0.7) Change, mean G1: – 2.3 vs. G2: – 2.3 *P* < 0.00002 **GDS**Baseline n G1: 15 G2: 15 Baseline score, mean (SD) G1: 11.7 (3.0) G2:12.3 (1.5) Change, mean (SD) G1: -3.2 G2: -6.0 *P<0.2*	
Author, Year McGrath et al., 2006[52] *Country, setting* United StatesPrimary care and psychiatric care practice settings *Funding* NIMH	*Study design* RCT *Type of analysis* ITT *N = 109* *Duration*	*TRD definition;* **"…**didnot achieve remission with, or were intolerant of, each of the first three levels of pharmacotherapy treatment." 3 failed treatments in current episode. Remission defined as HAM-D21 ≤ 7	*Subgroups* None *Treatment Failure* Failed 1 or more, 100% Failed 2 or more, 100% Current episode failures, mean 3 Mean failed trials 3	*HAM-D 17* Baseline n G1: 58 G2: 51 Baseline score, mean (SD) G1: 19.6 (7.6) G2: 19.7 (5.5) Endpoint score, mean (SD) NR:	*Quality of Life:* NA *Adverse Events:* NA *Neuropsychological or executive functioning:* NA *MMSE:* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective To compare the effectiveness and tolerability of tranylcypromine versus combination treatment with venlafaxine ER and mirtazapine in patients with treatment-resistant major depression. *Quality Rating:* Fair	12 -14weeks *Interventions* G1: Tranylcypromine G2: Venlafaxine ER + Mirtazapine *Parameters* G1: Tranylcypromine 10mg/d for 2wk, weekly increases of 10 mg/d until intolerance or 60 mg/d maximum G2: Venlafaxine ER + Mirtazapine: Venlafaxine 37.5 mg/d wk 1, 75 mg/d wk 2, 150 mg/d wks 3-5, 225 mg/d wks 6-8, 300 mg/d thereafter. Mirtazapine 15 mg/d wks 1-2, 30 mg/d next 8 wks, 45 mg/d thereafter *Strategy - switch*	*Setting(s)* *Genera and psychiatric settings* *Inclusion criteria* Primary diagnosis of nonpsychotic major depressive disorder by DSM-IV criteria; Did not achieve remission with or were intolerant of each of the first 3 levels of pharmacotherapy treatment in STAR*D *Exclusion criteria* NR *Stable psychotropic medications allowed* Not clearly reported	Previous treatment, not specified, 0% *Polarity, %* Unipolar Overall; 100% Bipolar I – 0% Bipolar II – 0% *Age, mean yrs* G1: 46.6 G2: 45.3 *Sex, % females* G1: 56.9 G2: 45.1 *Race, % white* G1: 79.3 G2: 84.3 *Right handed, %* Overall NR Groups similar at baseline – Overall yes. Groups received different medications at STAR*D level 3 treatment; difference in exiting Level 3 treatment due to intolerance of treatment, but these were controlled for in analysis. *Tier 1*	Responders, n NR Remitters, 7 or less, n (%) G1: 4 (6.9) G2: 7 (13.7) P= NS *QIDS SR* Baseline score, mean (SD) G1: 13.6 (5.1) G2: 14.9 (4.1) Endpoint score, mean (SD) G1: 12.3 (5.9) G2: 11.2 (5.6) Percent change G1: -6.2 (36.9) G2: -25.0 (30.4) *P* = NR Response 50% or greater improvement, n (%) G1: 7 (12.1) G2: 12 (23.5) *P* = NS Remitters, less than 5, n (%) G1: 8 (13.8) G2: 8 (15.7) *P* = NS	*Attrition:* NA *Adherence/ compliance:* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Poirier and Boyer, 1999[53] *Country, setting* France, Multi-center *Funding* Wyeth-Lederle, Paris France *Research Objective* Compare the efficacy and safety of venlafaxine and paroxetine in patients with treatment-resistant depression. *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 123 *Duration* 4 weeks *Interventions* G1: Venlafaxine G2: Paroxetine *Parameters* G1: Venlafaxine initiated at 37.5 mg twice daily and increased to 200 - 300 mg/day G2: Paroxetine initiated at 20mg/day and increased to 30 – 40 mg/day *Stable psychotropic medications allowed* No antipsychotics or MAOIs in last month; No anti coagulants, lithium, phenytoin, mood stabilizers or ECT. Stable anxioytics could be continued.	*TRD definition* • Resistance to two previous successive antidepressant treatments for current episode. • Remission defined as HAM-D17 <10 *Tier 1* *Setting(s)* Inpatient or Outpatient; *Inclusion criteria* • Inpatient or Outpatient; 18-60 years • Major Depression < 8 months old • HAM-D, 17 score ≥ 18 • TRD *Exclusion criteria* Use of venlafaxine or paroxetine for current episode; Hypersensitive to venlafaxine or paroxetine; Use of antipsychotics or monoamine oxidase inhibitors within previous month; Use of anticoagulants, lithium, phenytoin, mood stabilizers, or ECT; Anxioytics could continue if taken at stable dose	*Subgroups* None *Treatment Failure* Failed 1 or more, % 100 Failed 2 or more, % 100 Current episode failures, mean NR Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar NR Bipolar I NR Bipolar II NR *Age, mean yrs* G1: 42.5 G2: 44.1	*HAM-D 17* Endpoint score, calculated G1: 13.5 [OC] G2: 14.3 [OC] Change, mean (SD) G1: -11.1 (8.5) [OC] G2: -10.2 (6.8) [OC] OC, *P*= 0.55 ITT, *P* = 0.70 Average improvement NR Responders, n G1: 27 (44.3%) G2: 18 (29.0%) OC, *P* = 0.044 LOCF, *P* = 0.07 emitters, n G1: 22 (36.1%) G2: 11 (17.7%) OC, *P* = 0.01 ITT, *P* = 0.02 Other *BDI* NR *MADRS* NR *IDS* NR	*Quality of Life* NA *Adverse Events* NA *Neuropsychological or executive functioning* NA *MMSE* NA *Attrition* NA *Adherence/ compliance* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Switch *Diagnosis* 100% MDD	one month prior and continued through study; Mental disorder other than affective disorder; Suicidal ideation; Organic disease known as factor in TRD; Seizure disorders; Alcohol or drug dependence; Cardiac, renal, or hepatic disease; Pregnant; Breastfeeding; Women not using acceptable form of contraception	*Sex, % females* G1: 74 G2: 70 *P* = 0.59 *Race, % white* NR *Right handed, %* NR *HAM-D 17* Baseline n G1: 61 (LOCF), 52 (OC) G2: 62 (LOCF), 55 (OC) *Baseline score, mean (SD)* G1: 24.6 (3.9) G2: 24.5 (4.1) Groups similar at baseline Yes	*CGI-S* NR CGI-I Baseline n G1: 61 (LOCF), 52 (OC) G2: 62 (LOCF), 55 (OC) Average percentage improvement G1: 73% [OC] G2: 84% [OC] *P* = 0.39 Proportion of patients achieving a score of 1 or 2, n (%) G1: 33 (64) [OC] G2: 36 (66) [OC] *P* = NS LOCF results “look similar”	
Author, Year Shelton et al., 2005[54] *Country, setting* United States and Canada, multicenter (71 sites) *Funding* Eli Lilly and Company	*Study design* RCT *Type of analysis* Mixed-effects model repeated-measures regression *N* 500	*TRD definition* ≥ 1 past treatment failure to an SSRI after ≥ 4 weeks of therapy at a therapeutic dose. Failure was not required to be in current episode; and treatment failure during a 7 week nortriptyline dose-escalation lead-in period.	*Subgroups* Patients with an SSRI treatment failure during the current MDD episode. *Treatment Failure* Failed 1 or more, % 100 Failed 2 or more, % 100	*HAM-D 21* NR *BDI* NR *MADRS* Baseline n G1: 146 G2: 144 G3: 142 G4: 68	*Quality of Life* NA *Adverse Events* NA *Neuropsychological or executive functioning* NA *MMSE* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective To replicate findings within a larger patient sample, hypothesizing that olanzapine/fluoxetine combination would produce greater reductions in depressive symptoms than other treatment groups. *Quality Rating* Good	*Duration* 8 Weeks *Interventions* G1Olanzapine/fluoxetine combination G2: Olanzapine monotherapy G3: Fluoxetine monotherapy G4: Nortriptyline *Parameters* Olanzapine/fluoxetine combination = 25mg/d fluoxetine and 6mg/d olanzapine OR 50mg/d fluoxetine and 12mg/d olanzapine; Mean modal doses (SD) = 8.5 (3.1) olanzapine plus fluoxetine 35.6 (12.7) Olanzapine monotherapy = 6-12mg/d; Mean modal dose (SD)= 8.3(3.1) Fluoxetine monotherapy= 25-50mg/d; Mean modal dose (SD) = 35.8 (12.8) Nortriptyline = 25-175mg/d Mean modal dose (SD) = 103.5 (33.9)	So, 2 failed treatments (one in current episode) Failure defined as < 30% improvement in MADRS total score from baseline. Treatment response ≥ 50% decrease from baseline to endpoint in MADRS total score. Remission = 2 consecutive MADRS total scores ≤ 8. *Tier 1* *Setting(s)* NR *Inclusion criteria* Unipolar, nonpsychotic MDD Treatment failure as described above. MADRS total score ≥ 20 at both beginning and end of screening period. *Exclusion criteria* Concomitant medication with primary central	Current episode failures, mean NR Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar G1100 G2:100 G3:100 G4: 100 Bipolar I G10 G2:0 G3:0 G4: 0 Bipolar II G10 G2:0 G3:0 G4: 0 *Age, mean yrs* G142.5 G2:43.4 G3:41.7 G4:41.5	Baseline score, mean (SD) G1: 28.5 (7.5) G2: 28.4 (7.3) G3: 28.4 (7.3) G4: 28.8 (6.5) Week 0.5 Endpoint score, calculated G1: 24.87 G2: 24.62 G3: 25.88 G4: 25.85 Change, mean (SE) G1: -3.63 (0.65) G2: -3.78 (0.65); vs. G1: *P* = 0.868 G3: -2.52 (0.66); vs. G1: *P* = 0.230 G4: -2.95 (0.94); vs. G1: *P* = 0.555 Week 1 Endpoint score, calculated G1: 21.6 G2: 23.2 G3: 23.23 G4: 25.02 Change, mean (SE) G1: -6.90 (0.65) G2: -5.20 (0.65); vs. G1: *P* = 0.063 G3: -5.17 (0.66); vs. G1: *P* = 0.061 G4: -3.78 (0.95); vs. G1: *P* = 0.007	*Attrition* NA *Adherence/ compliance* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Switch	nervous system activity were not allowed with the exception of lorazepam. No other benzodiazepines were permitted. Patients developing psychotic symptoms during lead-in phase. Pregnant; Lactating; ECT treatment within 1 month or likely to require ECT during the study.	*Sex, % females* G167.1 G2:64.6 G3:72.5 G4: 67.6 *Race, % white* G190.4 G2:82.6 G3:90.8 G4: 88.2 *Right handed, %* G1NR G2:NR G3:NR G4:NR Groups similar at baseline Yes	Week 2 Endpoint score, calculated G1: 19.51 G2: 21.42 G3: 22.72 G4: 24.10 Change, mean (SE) G1: -8.99 (0.65) G2: -6.98 (0.65); vs. G1: *P* = 0.029 G3: -5.68 (0.66); vs. G1: *P* < 0.001 G4: -4.70 (0.95); vs. G1: *P* < 0.001 Week 3 Endpoint score, calculated G1: 19.28 G2: 20.85 G3: 22.30 G4: 23.47 Change, mean (SE) G1: -9.22 (0.65) G2: -7.55 (0.66); vs. G1: *P* =0.071 G3: -6.10 (0.67); vs. G1: *P* < 0.001 G4: -5.33 (0.95); vs. G1: *P* < 0.001 Week 4 Endpoint score, calculated G1: 18.56 G2: 20.54	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G3: 21.56 G4: 22.84 Change, mean (SD) G1: -9.94 (0.66) G2: -7.86 (0.66); vs. G1: *P* = 0.026 G3: -6.84 (0.68); vs. G1: *P* = 0.001 G4: -5.96 (0.95); vs. G1: *P* <0.001 Week 5 Endpoint score, calculated G1: 19.50 G2: 21.18 G3: 21.27 G4: 21.33 Change, mean (SE) G1: -9.00 (0.67) G2: -7.22 (0.67); vs. G1: *P* = 0.061 G3: -7.13 (0.68); vs. G1: *P* = 0.050 G4: -7.47 (0.95); vs. G1: *P* = 0.190 Week 6 Endpoint score, calculated G1: 19.14 G2: 21.00 G3: 20.31 G4: 20.25	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Change, mean (SE) G1: -9.36 (0.68) G2: -7.40 (0.69); vs. G1: *P* = 0.043 G3: -8.09 (0.69); vs. G1: *P* = 0.191 G4: -8.55 (0.96); vs. G1: *P* = 0.491 Week 7 Endpoint score, calculated G1: 19.59 G2: 21.54 G3: 20.49 G4: 20.18 Change, mean (SE) G1: -8.91 (0.69) G2: -6.86 (0.70); vs. G1: *P* = 0.036 G3: -7.91 (0.70); vs. G1: *P* = 0.305 G4: -8.62 (0.97); vs. G1: *P* = 0.805 Week 8 Endpoint score, calculated G1: 19.79 G2: 21.45 G3: 19.89 G4: 21.34 Change, mean (SE) G1: -8.71 (0.70) G2: -6.95 (0.71); vs. G1: *P* = 0.77 G3: -8.51 (0.70); vs. G1:	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				P = 0.841 G4: -7.46 (0.98); vs. G1: *P* = 0.298 Average percentage improvement NR Responders, n [calculated] (%, as reported in text) G1: 40 (27.5) G2: 27 (19.3) G3: 41 (28.9) G4: 20 (30.3) *P* = 0.18 Remitters, n [calculated] (%, as reported in text) G1: 24 (16.9) G2: 18 (12.9) G3: 18 (13.3) G4: 12 (18.2) *P* = 0.62 ** Of the 72 pts who remitted, 7 relapsed; No significant difference between groups *P* =0.21 Other: Post hoc Subgroup Analysis of pts with treatment failure during current MDD episode N=314	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Significant main effects for treatment (P = 0.004), for visit (P < 0.001), and for treatment-by-visit interaction (*P* = 0.04). *Endpoint score, calculated* G119.4 G2: 22.8 G3: 21.3 G4: 20.9 *Change, mean* G1: -9.1 G2: -5.6; vs. G1: *P* = 0.005 G3: -7.1; vs. G1: *P* = 0.18 G4: -7.9; vs. G1: *P* = 0.33 *IDS* NR *CGI-S* Baseline n G1: 146 G2: 144 G3: 142 G4: 68 Baseline score, mean (SE) G1: 4.4 (0.1) G2: 4.3 (0.1)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G3: 4.3 (0.1) G4: 4.4 (0.1) Endpoint score, calculated G1: 3.4 G2: 3.7 G3: 3.6 G4: 3.7 Change, mean (SE) G1: -1.0 (0.1) G2: -0.6 (0.1 G3: -0.7 (0.1) G4: -0.7 (0.1) P-Values: Overall: *P* = 0.048 G1: vs. G2: *P* = 0.006 G1: vs. G3: *P* = 0.088 G1: vs. G4: *P* = 0.131 *CGI-I* NR	
Author, Year Shelton et al., 2005[54] *Country, setting* NR, outpatient setting *Funding* NR *Research Objective:* To assess the efficacy and safety of olanzapine combined with	*Study design RCT* *Type of analysis ITT* *N = 28* *Duration* 8 weeks *Interventions* G1: Olanzapine + placebo (OLA) G2: Fluoxetine +	*TRD definition Failure* "…history of failure to respond to antidepressants of two different classes, one of which was not an SSRI, after at least 4 weeks of therapy at an acceptable therapeutic dose. Failure to respond was confirmed prospectively during a screening period in	*Subgroups - None* *Treatment Failure* Failed 1 or more, 100% Failed 2 or more, 100% Current episode failures, mean NR Mean failed trials Previous treatment, not specified, 0%	*HAM-D 21* Change, mean (SD) G1: -5.9 G2: -3.8 G3:-11.7 G3 vs. G1, *P* = 0.03 G3 vs. G2 (*P* = 0.07) *MADRS* Baseline n G1: 8 G2: 10 G3:10	*Quality of Life:* NA *Adverse Events:* NA *Neuropsychological or executive functioning:* NA *MMSE:* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
fluoxetine versus either agent alone in patients with recurrent major depressive disorder who were unresponsive to conventional antidepressant therapy. *Quality Rating* – Good	placebo (FLU) G3: Olanzapine + fluoxetine (COMBO) *Parameters* G1: Olanzapine + placebo (OLA): 5-20 mg/d G2: Fluoxetine + placebo (FLU): 20-60mg/d G3: Olanzapine + fluoxetine (COMBO): same dose as above *Strategy* – Augment (add OLA to FLU) or switch (to OLA)	which fluoxetine was given."; ≥ 2 *Tier 1* *Setting(s)* Outpatient *Inclusion criteria* • Met DSM-IV criteria for recurrent major depression without psychotic features • Resistant to conventional antidepressant pharmacotherapy • Score of greater to or equal to 20 on the HRSD-21 Exclusion criteria • History of psychosis, dysthymic disorder, or bipolar disorder	*Polarity, %* Unipolar 100% *Age, mean yrs - 42:* *Sex, % females - 75* *Race, % white - 96* Groups similar at baseline Unclear; only #'s are reported *HAM-D 21* Baseline n G1: (OLA): 8 G2 (FLU): 10 G3 (COMBO):10 Mean baseline severity not reported, but eligibilty criteria required that 21-item HAM-D was ≥ 20,	Change, mean (SD) G1: -2.8 G2: -1.2 G3:-13.6 Responders, n (%) G1: 0 (0) G2: 1 (10) G3:6 (60) G3 vs. G1, *P* = 0.03 G3vs. G2, *P* = 0.11	*Attrition:* NA *Adherence/ compliance:* NA
Author, Year Thase, 2007[55] *Country, setting* United States and Canada *Funding* Eli Lilly and Co.	*Study design* RCT; 2 identical concurrent studies; sites were randomly assigned to either Study 1 or Study 2. *Type of analysis* ITT	*TRD definition* "Failure to achieve satisfactory response to an antidepressant (except fluoxetine) after at least 6 weeks at a therapeutic dose occurring within the current episode of MDD." Second failure occurred during, "an 8-	*Subgroups* None *Treatment Failure* Failed 1 or more, % 100% Failed 2 or more, % 100%	*HAM-D 21* NR *BDI* NR *MADRS* Baseline n (both studies combined) G1: 200 G2: 206 G3:200	*Quality of Life* NA *Adverse Events* NA *Neuropsychological or executive functioning* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective Examine the efficacy and tolerability of olanzapine/fluoxetine combination, olanzapine and fluoxetine in outpatients with 2 treatment failures during the current mood episode. *Quality Rating* Fair	*N* 605 *Duration* 8 weeks *Interventions* G1: Olanzapine/Fluoxetine Combination G2:Fluoxetine G3: Olanzapine *Parameters* G1: Olanzapine 6, 12, or 18 mg/day + 50 mg/day fluoxetine G2: Olanzapine 6, 12, or 18 mg/day G3: Fluoxetine 50 mg/day *Strategy* Switch	week open-label lead-in phase to establish fluoxetine resistance." *Setting(s)* Outpatient *Inclusion criteria* 18-65 years; HAM-D17 ≥ 22; Diagnosis of MDD, recurrent, without psychotic features; Failure to 6 week antidepressant therapy within current episode of MDD; Failure to exhibit response to fluoxetine during 8 week lead-in phase. *Exclusion criteria* Schizophrenia; Schizoaffective disorder; Psychotic disorders, Bipolar disorder; Posttraumatic stress disorder; Dissociative disorders; Pregnant; Breast0feeding; Postpartum depression; MDD with atypical features; MDD with seasonal pattern; Paranoid, schizoid, schizotypal, antisocial, severe borderline personality disorder; Significant medical	Current episode failures, mean NR Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar G1100% G2:100% G3:100% Bipolar I G2: 0 G3: 0 G1: 0 Bipolar II G1: 0 G2: 0 G3:0 *Age, mean yrs* Study 1 G1: 43.3 G2: 44.8 G3: 45.7 Study 2 G1: 45.3 G2: 44.5 G3: 43.0	Study1 Baseline score, mean (SD) G1: 29.5 (7.1) G2: 29.7 (6.9) G3: 29.7 (7.1) Study 2 Baseline score, mean (SD) G1: 30.6 (6.1) G2: 30.1 (5.9) G3: 30.1 (6.3) Pooled Baseline score, mean (SD) G1: 30.0 (6.7) G2: 29.9 (6.4) G3: 29.9 (6.7) Study1 Endpoint score, calculated G1: 18.7 G2: 20.3 G3: 19.6 Study2 Endpoint score, calculated G1: 16.0 G2: 21.1 G3: 22.4 Pooled Endpoint score, calculated	*MMSE* NA *Attrition* NA *Adherence/ compliance* NA

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		illness; Concomitant medications with primary central nervous system activity Interim Exclusion Criteria: Response to fluoxetine during lead in prior to randomization or presentation of psychotic features.	Pooled G1: 44.3 G2: 44.6 G3: 44.3 *Sex, % females* Study 1 G1: 61.8 G2: 58.7 G3: 58.3 Study 2 G1: 70.4 G2: 65.7 G3: 65.0 Pooled G1: 66.0 G2: 62.1 G3: 61..8 *Race, % white* Study 1 G1: 85.3 G2: 83.7 G3: 76.0 Study 2 G1: 91.8 G2: 88.2 G3: 88.3 Pooled G1: 88.5 G2: 85.9 G3: 82.4 *Right handed, %* G1: NR	G1: 17.4 G2: 20.7 G3: 21 Study 1 Change, mean (SD) G1: -10.8 (10.0) G2: -9.4 (9.9) G3:-10.1 (9.6) P-values: Overall, *P* = 0.640 G1: vs. G2, *P* = 0.346 G1: vs. G3, *P* = 0.624 Study 2 Change, mean (SD) G1: -14.6 (10.2) G2: -9.0 (9.5) G3: -7.7 (8.2) P-values: Overall, *P* < 0.001 G1: vs. G2, *P* < 0.001 G1: vs. G3, *P* < 0.001 Pooled Change, mean (SD) G1: -12.6 (10.3) G2: -9.2 (9.7) G3: -8.9 (9.0) P-values: Overall, *P* < 0.001 G1: vs. G2, *P* < 0.001 G1: vs. G3, *P* < 0.001 Study 1 Responders, n (%) G1: 37 (36.6) G2: 30 (29.4)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
			G2: NR G3:NR Groups similar at baseline Yes *Tier* Tier 1	G3: 34 (35.8) Overall *P* = 0.496 Study 2 Responders, n (%) G1: 43 (44.3) G2: 30 (29.7) G3: 17 (16.7) Overall *P* <0.001 Pooled Responders, n (%) G1: 80 (40.4) G2: 60 (29.6) G3: 51 (25.9) Overall *P* = 0.006 G1: vs. G2, *P* = 0.028 G1: vs. G3, *P* = 0.003 Study1 Remitters, n (%) G1: 24 (23.8) G2: 18 (17.6) G3: 18 (18.9) Overall *P* = 0.522 Study 2 Remitters, n (%) G1: 30 (30.9) G2: 16 (15.8) G3: 11 (10.8) Overall *P* = 0.001 Pooled Remitters, n (%) G1: 54 (27.3) G2: 34 (16.7) G3: 29 (14.7)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Overall *P* = 0.004 G1: vs. G2, *P* = 0.012 G1: vs. G3, *P* = 0.003 Other IDS CGI-S Baseline n (both studies combined) G1: 200 G2: 206 G3:199 Study 1 Baseline score, mean (SD) G14.5 (0.7) G2: 4.7 (0.7) G3: 4.6 (0.7) Study 2 Baseline score, mean (SD) G1: 4.7 (0.7) G2:4.7 (0.7) G3: 4.7 (0.7) Pooled Baseline score, mean (SD) G1: 4.6 (0.7) G2: 4.7 (0.7) G3: 4.7 (0.7)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Study 1 Endpoint score, calculated G1: 3.4 G2: 3.7 G3: 3.5 Study 2 Endpoint score, calculated G1: 3.2 G2: 3.6 G3: 3.9 Pooled Endpoint score, mean (SD) G1: 3.3 G2: 3.7 G3: 3.8 Study 1 Change, mean (SD) G1: -1.1 (1.3) G2: -1.0 (1.2) G3:-1.1 (1.1) Overall, *P* = 0.681 G1: vs. G2, *P* = 0.384 G1: vs. G3, *P* = 0.722 Study 2 Change, mean (SD) G1: -1.5 (1.3) G2: -1.1 (1.2) G3: -0.8 (1.1) Overall, *P* < 0.001 G1: vs. G2, *P* = 0.004 G1: vs. G3, *P* < 0.001	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Pooled Change, mean (SD) G1: -1.3 (1.4) G2: -1.0 (1.2) G3: -0.9 (1.1) Overall, *P* = 0.003 G1: vs. G2, *P* = 0.008 G1: vs. G3, *P* = 0.001 *CGI-I* NR *Brief Psychiatric Rating Scale (BPRS)* Baseline n (both studies combined) G1: 200 G2: 206 G3:199 Study 1 Baseline score, mean (SD) G1: 17.1 (7.7) G2: 17.6 (7.7) G3: 16.1 (6.5) Study 2 Baseline score, mean (SD) G1: 15.2 (5.7) G2: 15.3 (5.6) G3: 14.8 (5.5) Pooled Baseline score, mean (SD)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G1: 16.2 (6.8) G2: 16.5 (6.8) G3: 15.4 (6.0) Study 1 Endpoint score, calculated G1: 11.7 G2: 12.8 G3: 11.8 Study 2 Endpoint score, calculated G1: 9.3 G2: 11.0 G3: 12.4 Pooled Endpoint score, calculated G1: 10.6 G2: 11.9 G3: 12.1 Study 1 Change, mean (SD) G1-5.4 (7.5) G2: -4.8 (7.7) G3: -4.3 (7.4) Overall, *P* = 0.646 G1: vs. G2, *P* = 0.562 G1: vs. G3, *P* = 0.357 Study 2 Change, mean (SD) G1: -5.9 (6.8) G2: -4.3 (6.1) G3: -2.4 (6.2)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Overall, *P* = 0.001 G1: vs. G2, *P* = 0.058 G1: vs. G3, *P* < 0.001 Pooled Change, mean (SD) G1: -5.6 (7.2) G2: -4.6 (7.0) G3:-3.3 (6.8) Overall, *P* = 0.009 G1: vs. G2, *P* = 0.097 G1: vs. G3, *P* = 0.002	

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] Avery 2007[11] *Country, setting* USA, Single center, University department of psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint Interventions G1: High-left rTMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous rTMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence withinpast 2 years,	*Subgroups* Pain, subgroup analysis presented in Avery et al, 200711 *Baseline n* G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 Age, mean yrs G1: 44.3 G2: 44.2 Sex, % females G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR Groups similar at baseline Yes	*HAM-D 17* Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time *P* = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) *P* = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) *P* = 0.033 HAM-D 17 6- month relapse, n (%) G1: 6 (54.5); 1 lost to follow up G2: 1 (50); 1 lost to follow up *P*= NR *G1* *G2:BDI* Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, *P* < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity	*HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)	Random Regression analyses revealed significant group by time interaction (P = 0.003)	*Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% (P < 0.05) No statistically significant (P > 0.05) time by treatment group interactions for any of neuropsychological test measures.models were refit withoutinteraction term, there was no significant treatment group main effect (P > 0.05) evident for any ofneuropsychological tests, indicatinggroups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session. *MMSE* NR *Attrition* Overall, % 7.4% (5/68) At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adherence/ compliance NR
Author, Year Boutros et al., 2002[13] *Country, setting* US, Yale School of Medicine and VA-Connecticut, outpatient *Funding* VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer *Research Objective* To provide additional data on effiacy and safety for rTMS as an augment strategy in TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 21 *Duration* 2 weeks txt; follow-up with responders for up to 20 weeks post txt Interventions G1: rTMS G2: Sham *Medications Allowed* • Pts allowed to continue all current psychotropic meds *Strategy* Augmentation, 3 pts in active and 1 in sham txt were not on any meds Parameters rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 58	*TRD definition* • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major Depression • HAM-D25 >= 20 *Exclusion criteria* • Suicidality • "Prominent" psychotic sympotms • History of neurological disorders • current drug abuse	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 100% Age, mean yrs G1: 49.5 G2: 52.0 Sex, % females G1: 25 G2: 10 Right handed, % G1: 90.9 G2: 88.9 *HAM-D* Baseline n G1: 12 G2: 9 Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)	*HAM-D 25* Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 *P* = NS Responders, n Defined as 30% improvement on Ham-D 25 G1: 7 G2: 2 Responders, n (%) Defined as 50% improvement on Ham-D 25 G1: 3 G2: 2 *Relapse* Defined as ≥ baseline score ± 10% Of 6 active treatment responders inluded in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in	*Quality of Life* NR *Adverse Events* Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6 Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR *Attrition* Overall, % 18.2% (4/22) At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10) At end of follow-up, % NR

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp			the 20-week follow-up, 1 relapsed.	Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR *Adherence/ compliance* NR

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Berman et al., 2000[28] *Country, setting* US, urban community health center, inpatient and outpatients *Funding* Veterans Administration, NIMH, State of CT *Research Objective* To assessefficacy of rTMS in unmedicated TRD patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 20 *Duration* 2 weeks (10 weekdaysof txt) Primary outcome = HAM-D 25 at 2 wks Interventions G1: rTMS G2: Sham rTMS *Medications Allowed* All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep *Strategy* Switch *Parameters* rTMS – LDLPFC • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval:58	*TRD definition* • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imiprimine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode *Tier 2* *Inclusion criteria* • Current Major depressive episode (perHAM-D) *Exclusion criteria* • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control	*Treatment Failure* Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup) *Polarity, %* Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 Age, mean yrs G1: 45.2 G2: 39.4 Sex, % females G1: 20 G2: 40 Race, % white G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic) *HAM-D 25* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 37.1 G2: 37.3	HAM-D 25 G1: rTMS G2: Sham TMS Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) P < 0.05 Responders, n 50% decrease from baseline and score ≤, 15 G1: 1 (10) G2: 0 P = 0.09 2-month maintained response, n % G1: 1 (100) G2: 0 (100) P=NR Three partial responders symptom severity returned to baseline within 1-2 weeks BDI Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) P = 0.27\\\	*Quality of Life* NR *Adverse Events* Headache, n G1: 60 G2: 50 Difficulty starting urination great in active group *P* = 0.03 Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appétit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Pulses per session:800 • Total number of sessions: 10 in 10 days Sham • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp				coordination, and muscle stiffness *MMSE* NR *Attrition* Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0 *Adherence/ compliance* NR

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year O'Reardon, 2007[31] Janicak, 2007[56]* Sovason, 2007[57] Janicak 2010[58] *Country, setting* US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported *Funding* Neuronetics *Research Objective* To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral perfrontal cortex is effective and safe inacute treatment of major depression and to determine whether the benefit of TMS dissipates over a clinically meanignful duration of follow-up *Quality Rating* Good	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 325 randomized; Continuation of 67 responders from original 301 patientsincluded in final analysis; 99 with rTMS response compared with 21 sham responders in durability study *Duration* 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over after 4 weeks if not responding. 24 weeks; open-label continuation of effect study Interventions G1: Active TMS G2: Sham TMS *Medications Allowed* All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use	*TRD definition* • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime *Tier 2 Setting(s)* Not clearly reported *Inclusion criteria* • Aged 18—70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed atscreening assessment *Exclusion criteria* • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder	Baseline N (ContinuationStudy) G1: 165 (44) G2: 160 (23) Current episode failures, meanG1: 1.6 G2: 1.6 Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar 100 Age, mean yrs (Continuation Study) G1: 47.9 (49.2) G2: 48.7 (48.6) Sex, % females (Continuation Study) G1: 55.5% (54.5%) G2: 50.7% (47.8%) Race, % white (Continuation Study) G1: 94.2% (88.6%) G2: 89.7% (82.6%) *HAM-D 17* Baseline score, mean (SD); Continuation Study G1: 22.6 (3.3); 6.5 (4.8) G2: 22.9 (3.5); 7.5(5.0)	*HAM-D 17* Analyzed n (Continuation study) G1: 155 (37) G2: 146 (19) Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5 At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0) Change, mean (SD) At week 2 G1: -5.2 G2: -3.5 At week 4 (Continuation Study) G1: -14.6 (6.16) G2: -14.4 (6.11) At week 6 G1: -5.5 G2: -3.3 *P* = 0.005 At week 24 (Continuation Study) G1: -15.4(6.11) G2: -17.3 (5.07)	*Quality of Life* Medical Outcomes Study Short Form-36 (MOS SF-36) Baseline n G1: 155 G2: 146 Baseline score, mean (SD) Mental Component Score G1: 20.4 (8.05) G2: 20.4 (7.76) Physical Component Score G1: 50.5 (11.01) G2: 48.8 (10.35) Endpoint Score NR Change, mean (SD) Mental Component Score At week 4 G1: 4.5 (10.16) G2: 2.0 (9.42) *P* = 0.019 At week 6 G1: 5.7 (12.65) G2: 2.9 (10.6) *P* = 0.032

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	hypnotics, anxiolytics for txt emergent insomnia or anxiety *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks; For add-on rescue treatment 2/week for 2wks then 5/week for 4wks rTMS Sham: • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil	• Posttraumatic stress disorder and eating disorders (if present in past year) • Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head	*MADRS* Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 32.8 (6.0); 9.0(8.2) G2: 33.9 (5.7); 10.9(8.1) *IDS* Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 42.0 (9.4); 14.4(9.8) G2: 43.4 (9.9); 13.4(9.4) CGI-S Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 4.7 (.6); 1.9(1.2) G2: 4.7 (.7); 2.3(1.0)	Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9) *P* > 0.10 At week 4 G1: 32 (20.6) G2: 17 (11.5) *P* < 0.05 At week 4 (continuation study) G1: 30(68.2) G2: 13 (56.5) At week 6 G1: 38 (24.5) G2: 20 (13.7) *P* < 0.05 At week 24 (continuation study) G1: 24(54.5) G2: 12(52.5) Remission rate n (%) HAM-D17 < 8 At week 2 G1: 5 (3.2) G2: 3 (2.1) *P* > 0.10 At week 4 G1: 110 (7.1) G2: 9 (6.2) *P* > 0.10	Physical Component At week 4 G1: 0.3 (7.52) G2: 0.2 (7.28) *P* = 0.892 At week 6 G1: 0.1 (7.49) G2: -0.2 (7.23) *P* = 0.682 Quality of Life, Enjoyment and Satisfaction Questionnaire –Short Form (Q-LES-Q) Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 37.8 (8.23) G2: 36.5 (7.87) Endpoint score, mean (SD) At week 4 G1: 41.4 (10.32) G2: 39.0 (9.78) At week 6 G1: 42.2 (12.28) G2: 39.0 (10.15)

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At week 4 (continuation study) G1: 19(43.2) G2: 10(43.5) At week 6 G1: 24 (15.5) G2: 13 (8.9) *P* = 0.065 At week 24 (Continuation Study) G1: 18 (40.9) G2: 10(43.5) MADRS Endpoint score, mean (SD) At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1) At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8) Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1 At 4 weeks (Continuation Study) G1: -21.2 (10.42) G2: -20.2(10.43) At 6 weeks G1: 6 G2: 3.9	Change, mean (SD) At week 4 G1: 3.50 (9.19) G2: 3.80 (11.58) At week 6 G1: 2.0 (9.24) G2: 1.3 (9.85) Other Active rTMS vs. Sham *P* = 0.035 at week 6 *Adverse Events* Serious adverse events G1: 6 G2: 5 Suicidality, % G1: 0.6 G 2: 1.9 Exacerbation of depression, % Active TMS: 0.6 Sham TMS: 1.9% Eye pain: active, % TMS: 6.1 Sham TMS: 1.9%; GI disorders toothache, % Active TMS: 7.3 Sham TMS: 0.6

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At week 24 (Continuation Study) G1: -23(9.27) G2: -24.6(8.81) Response rate, % At week 2 G1: 8.4 G2: 6.2 *P* > 0.10 At week 4 G1: 18.1 G2: 11.0 *P* <0.05 At week 4 (Continuation Study) G129(65.9) G2: 12 (25.2) At week 6 G1: 23.9 G2: 12.3 *P* <0.01 At week 24 (continuation study) G1: 24 (54.5) G2: 11(47.8) Remission rate, % Remission defined as total score <10 At week 2 G1: 3.9 G2: 2.1 *P* > 0.10	Application site discomfort, % TMS: 10.9 Sham: 1.3% Application site pain, %: TMS: 35.8 Sham: 3.8 Facial pain, % Active TMS: 6.7 Sham TMS: 3.2 Muscle twitching, % TMS: 20.6 Sham: 3.2 Pain of skin, % TMS: 8.5 TMS: 0.6% Adverse Events (Continuation Study)Constipation: G1: 0 G2: 0 Dry Mouth: G1: 0 G2: 0 Application Site Pain: G1: 6.8%G2: 26.1% Arthralgia: G1: = 2.3%, G2 = 0 Muscle Twitching: G1: = 4.5%, G2 = 13.0% Headache: G1: = 6.8%, G2 = 8.7%

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At week 4 G1: 7.1 G2: 6.2 *P* > 0.10 At week 4 (Continuation Study) G1: 20(45.5) G2: 11(47.8) At week 6 G1: 14.2 G2: 5.5 *P* < 0.05 At week 24 (continuation study) G1: 18(40.1) G2:9(39.1) Other Relapse Rates: Relapse defined as recurrence of MDD per DSM-IV ≥ 2 weeks (HAM-D 17 ≥ 20; CGI-S ≥ 4) At week 4 (continuation study) G1: 2.3% G2: 7.8% At week 24 (continuation study) G1: 7.8% G2: 15.0%	Insomnia: G1: 0 G2: 0 MMSE NR *Attrition* Overall, % 15 At end of treatment, % G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6% At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0.6% G2: 1% Withdrawals due to adverse events, % G1: 5% G2: 4% Other 325 subjects were randomized 24 were "nonevaluable" 301 continued to receive at least 1 treatment, these 301 were included in final analysis 277 completed study through week 4.

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Symptomatic Worsening (% experiencing worsening) G1: 36.4% G2: 47.8% Kaplan-Meier Survival estimate of symptomatic deterioration G1: 37.4% G2: 60.8% In durability study combining rTMS responders Relapse, n (%) G1: 10 (10) G2: 3 (13.6)	*Adherence/ compliance* NR
Author, Year Stern et al., 2007[32] *Country, setting* NR, outpatient setting *Funding* The Milton Fund, NARSAD,Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Cienca *Research Objective* To testhypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC)	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in the analysis *N* 45 *Duration* • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse.	*TRD definition* • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode *Tier 2* *Inclusion criteria* • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20 *Exclusion criteria* • H/O any psychotic disorder (incl. schizophrenia or	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100 % MDD Age, mean yrs G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3 Sex, % females G1: 60 G2: 60 G3: 70 G4: 60 *Right handed, %* 100	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6) Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3)	*Quality of Life* NR *Adverse Events* 9/45 pts reported severe headaches (pts by group NR); no seizures *Attrition* Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an *Quality Rating* Fair	Primary Outcome: HAM-D at 2 weeksnd and 2 weeks after treatment Interventions G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz toright DLPFC G4: Sham rTMS *Medications allowed* No psychotropic medications were allowed *Parameters* rTMS High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1	schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy	*HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10 G4: 15 Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)	Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3) Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, *P* = 0.001 2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, *P* = 0.00001 Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0 At week 2 G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 (*P* < 0.0005)	Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period. Reported in text as dropped out following week 2. *Adherence/ compliance* NR

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Sham rTMS: • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above *Strategy* Switch			1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 (P < 0.0005) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1/G3 vs. G2/G4 (P < 0.0005) Remitters, n HAM-D ≤ 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%) G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%)	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 *P* = NS (all times); G2 vs. G4 and G1: vs. G3 *P* = NS (all times)	
Author, Year Bortolomasi et al., 2006[34] *Country, setting* Italy, single center, inpatient vs. outpatient NR *Funding* Not reported *Research Objective* To investigate outcome of depressed patients treated for 1 month with high frequency rTMS onleft frontal lobe at long time periods *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 19 *Duration* Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article Interventions G1: rTMS G2: Sham	*TRD definition* • Drug resistance (not defined) • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations *Exclusion criteria* • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar G1: 83.3 G2: 85.7 Bipolar G1: 16.7 G2: 14.3 Age, mean yrs G1: range 45-56 G2: range 44-53 Overall: 55.6 Sex, % females G1: 58 G2: 57 *Race, % white* NR	*HAM-D 24* Endpoint score, mean (SD) At week 1 G1: 11.33 G2: 18.29 At week 4 G1: 11.42 G2: 19.14 At week 12 NR Change, mean (SD) At week 1 G1: -13.84 G2: NR *P* = NR, significant	*Quality of Life* NR *Adverse Events* No adverse effects were reported in either group, except for mild cephalgia by 3 patients treated with anti-inflammatory drugs Headache, % • 3 patients reported mild headaches after treatment • All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Medications allowed Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry) *Strategy* Augmentation Allowed to continue on failed SSRIs (63.2%) and TCAs (26.3%), No meds (5.3%) *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil Sham • Stimulation coil was placed perpendicular tothe scalp surface without direct contact. Coil position was fixed for all TMS sessions,		*Right handed, %* Overall: 100 Groups similar at baseline Yes *Tier* *HAM-D 24* Baseline n G1: 12 G2: 7 Baseline score, mean (SD) G1: 25.17 G2: NR	Group x time at wk 2 and 4, $P < 0.05$ At week 4 G1: -13.75 G2: NR At week 12 NR IG1: rTMS G2: Sham Baseline n G1: 12 G2: 7 Baseline score, mean (SD) G1: 25.42 G2: NR Endpoint score, mean (SD) At week 1 G1: 12.25 G2: 22.43 At week 4 G1: 11.67 G2: 24.57 Change, mean (SD) At week 1 G1: 13.17G2: NR At week 4 G1: 13.75 G2: NR	after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep. • 3 patients reported mild headaches after treatment *Attrition* NR *Adherence/ compliance* NR

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	and stimulation at this site evoked minimal motor activity				
Author, Year McLoughlin et al., 2007[7] Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); byGuy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating	*Study design* RCT- pragmatic and single blinded (raters) *Type of analysis* m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months Interventions G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % Age, mean yrs G1: 63.6 G2: 68.3 Sex, % females G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0) *BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93 Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End ot treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
major depressive episodes in patients referred for ECT *Quality Rating* Good	*Strategy* Augmentation *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions: daily for 15 days ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5			Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25 Responders, n NR Remitters, n NR	suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR *Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales (verbal fluency,

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					anterograde memory, and retrograde memory) *MMSE* Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects. Attrition Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR
Author, Year Paykel, 1999[38] Scott, 2000[59] Scott, 2003[60] Paykel, 2005[61] Note: #2223, #2219, #274, and #3815 are companion studies, data was abstracted in toform for #2219. *Country, setting* UK, outpatient Retrospective analysis: Inpatient or Outpatient *Funding* Medical Research Council, London, England and a grant fromOxford and Anglia Region *Research Objective* To compare cognitive	*Study design* RCT *Type of analysis* ITT *N* 158 Retrospective analysis: 135 *Duration* Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks. Retrospective analysis: wks 69 and onward (up to 6 years)	*TRD definition* • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months.	*Treatment Failure* Mean failed trials G1: NR G2: NR Retrospective analysis: G3: NR G4: NR *Polarity, %* Unipolar 100% Retrospective analysis: G3: NR *G4: NRAge, mean yrs* G1: 43.2 (11.2) G2: 43.5 (9.8) Retrospective analysis: G3: 48.6 G4: 49.8 *Sex, % females* G1: 53% G2: 46%	*HAM-D 17* G1: Clinical Management only G2: CT plus Clinical Management Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2) Follow up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7) Follow up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3) Retrospective analysis: Mean scores at end of study G3: 7.3 (5.5) G4: 8.0 (6.4)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 20% did not adhere to protocol through to study end or relapse point Retrospective analysis: 14.5% Reasons for Overall Attrition: Deceased, n= 7; Refused, n = 11; Non-response to request, n = 3, Not traceable, n = 2 At end of treatment, % G1: 4 G2: 14

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintainance treatment with antidepressants. Retrospective analysis: To restudy subjects approximately 6 years after randomization, or 4 1/2 years after completion of the trial and its follow-up phase *Quality Rating* Fair	*Interventions* G1: Clinical management Only G2: CT plus Clinical Management Retrospective Analysis G3: Clinical management only G4: CT plus Clinical Management *Medications allowed* Continued on current medications with dose adjustments allowed *Strategy* Augmention *Parameters* Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16	• Failure required to be in the current episode • Retrospective Analysis Relapse defined as return to Major depression for 4 wks or, during the follow-up trial phase only, persistent residual symptoms for at least 8 weeks reaching 13 on the HAM-D in two successive rating 8 wks apart and producing a sufficient level of distress or dysfunction to mandate withdrawal from treatment constraints. *Tier 2* *Inclusion criteria* • Unipolar depression, • aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression withinlast 18 months but not inlast 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase	Retrospective analysis: G3: 52% G4: 50% *HAM-D 17* Baseline n G1: 78 G2: 80 Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7) *BDI* Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)	Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 *P* = NS Follow up at 44 weeks G1: - 3.0 G2: -4.5 Follow up at 68 weeks G1: -5.0 G2: -4.9 Responders, n NR Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45)) Retrospective analysis: Remission by 68 weeks G3: 30 G4: 42 *BDI* Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6),	At end of followup, % G1: 12 G2: 10 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		inhibitor for at leastprevious 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. *Exclusion criteria* • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, • any other primary Axis I disorder attime ofindex illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT		Follow up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3) Follow up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7) Change, mean (SD) At week 20 G1: -6.24 G2: -8.44 Responders, n NR Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%) Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36) Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		for more than 5 sessions.		Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI (0.32, 0.93). Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219: Relapse was defined as: (1) meetingDSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms during follow up phase between 2 successive ratings 2 months apart, reaching	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				a score onHAM-D 17 of at least 13 on both occassions and a level of distress or dysfunction for which the withholding of additional active treatment was no longer justified Retrospective Analysis Acutarial Kaplan-Meier recurrence rates (%): Wk 20 (from randomization): G1: 24 G2: 5 Difference (95% CI), p-value: 19 (8 to 30), p = 0.002 Wk 68 (from randomization): G1: 34 G2: 23 Difference (95% CI), p-value: 11 (-3 to 25), p = 0.07 Wk 120(from randomization): G1: 43 G2: 83 Difference (95% CI), p-value: 5 (-11 to 21), p = 0.25 Wk 172 (from randomization): G1: 49 G2: 41	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Difference (95% CI), p-value: 8 (-8 to 24), p = 0.16 Wk 224 (from randomization): G1: 55 G2: 56 Difference (95% CI), p-value: -1 (-17 to 15), p = 0.52 Wk 275 (from randomization): G1: 65 G2: 60 Difference (95% CI), p-value: 5 (-11 to 21), p = 0.33	

*This study came from an unpublished source (conference proceeding).

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Grunhaus et al., 2000[62] *Country, setting* Israel Sheba Medical Center, inpatients and outpatients *Funding* Established Investigator Award of NARSTAD *Research Objective* To compare rTMS to ECT and psychotic vs. non-psychotic *Quality Rating* Poor	*Study design* RCT *Type of analysis* ITT *N* 40 *Duration* Varied – ECT patients treated for average of 5 weeks, and rTMS pts treated for 4 weeks. Primary outcome measured at end of treatment *Interventions* Overall G1: ECT G2: rTMS Pts with psychosis G3: ECT: G4: rTMS Pts without psychosis G5: ECT G6: rTMS *Medications allowed* • ECT allowed benzodiazepines, neuroleptics antidepressants and anticonvulsants in stable doses	*TRD definition* • Pts referred for ECT • Only some patients treatment resistant (not defined). Treatment failure not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • age over 18 • DSM-IV diagnosis of MDD • HAM-D17 ≥18 • no personal or first-degree relative history of seizure • no medical, neurological, or neurosurgical disorder that would precludeadministration of ECT or rTMS. *Exclusion criteria* • Additional Axis-1 diagnoses	*Subgroups* Patients with and with out Psychosis *Treatment Failure* Failed ≤1 trial, % G1: 50 G2: 25 Failed ≥2 trials, % G1: 50 G2: 75 *Polarity, %* 100% MDD *Age, mean yrs* G1: 63.6 (15.0) G2: 58.4 (15.7) *Sex, % females* G1: 70 G2: 60 *HAM-D 17* Baseline n Overall G1: 20 G2: 20 Patients with Psychosis G3: 10 G4: 9 Patients without Psychosis G5: 10 G6: 11	*HAM-D 17* Endpoint score, mean (SD) At week 2 G1: 17.6 (7.4) G2: 19.3 (8.6) G3: 15.5 (7.6) G4: 23.4 (5.5) G5: 19.7 (7.0) G6: 15.8 (9.3) End of treatment G1: 11.2 (8.4) G2: 15.4 (7.5) G3: 8.4 (5.3) G4: 20.8 (5.0) G5: 13.9 (10.3) G6: 11.0 (6.2) Change, mean (SD) At week 2 G1: 10.8 G2: 6.5 G3: 16.0 G4: 5.3 G5: 5.5 G6: 7.7 End of treatment G1: 17.2 G2: 10.4 Group x time, *P* = 0.09 G3: 23.1 G4: 7.9 Group x time, *P* = 0.005 G5: 11.3 G6: 12.5 Group x time, *P* = NS	*Quality of Life* Scale Pittsburg Sleep Quality Index Intervention G1: ECT G2: rTMs G3: G4: ECT Psychotic vs none G5: rTMS Psychotic vs none Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11 Baseline score, mean (SD) G1: 12.5 (4.4) G2: 11.7 (5.7) G3: G4: 12.1 (5.5) vs 12.9 (3.1) G5: 14.1 (4.9) vs 9.7 (5.8) Endpoint score, mean (SD) G1: Awk2 8.8 (4.5)/endpoint 6.8 (3.5)

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• rTMS All psychiatric medications were discontinued only clonazepam (1–2 mg/day, given in twice-daily doses) was started in all patients to decrease anxiety, provide relief of severe insomnia, and have an additional protective element regarding seizures *Strategy* Mixed-between group differences *Parameters* ECT: • % receiving bilateral: 40 switched after non-response • Intensity 2.5-fold seizure threshold • Number of sessions - mean 9.6 sessions (range 7-14) rTMS Low • Frequency (Hz): • Motor threshold (%): • Number of trains: • Length of train (seconds): • Inter-train interval:		Baseline score, mean (SD) G1: 28.4 (9.3) G2: 25.8 (6.1) G3: 31.5 (11.5) G4: 28.7 (5.6) G5: 25.2 (5.3) G6: 23.5 (5.6)	Responders if the final HRSD had decreased to 50% or more from baseline and the final GAS < 60. Responders, n End of txt G1: 16 (80%) G2: 9 (45%) *P* < 0.05 G3: 10 (100%) G4: 2 (22%) *P* ≤ 0.01 G5: 6 (60%) G6: 7 (63%) *P* = NS	G2: Awk2 10.1 (3.7)/endpoint 10.5 (3.9) G3: G4: Awk2 8.0 (4.5)/endpoint 5.8 (2.1) vs Awk2 8.0 (4.5)/endpoint 5.8 (2.1) G5: Awk2 12.2 (2.8)/endpoint 12.3 (3.6) vs. Awk2 8.4 (3.5)/endpoint 9.1 (3.8) Change, mean (SD) G1: Awk2 3.7/endpoint 5.7 G2: Awk2 1.6/endpoint 1.2 G3: G4: Awk2 4.1/endpoint 6.3 vs Awk2 4.9/endpoint 7.1 G5: Awk2 11.9/endpoint 1.8 vs. Awk2 1.3/endpoint 0.6 Other Overall Group F 1.8 (df 1,36) *P* = NS Time F 12.5 (df 2,72) *P* = 0.000

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Pulses per session: • Total number of sessions: rTMS High • Frequency (Hz): • Motor threshold (%): • Number of trains: • Length of train (seconds): • Inter-train interval: • Pulses per session: • Total number of sessions:				Interaction F 4.6 (df 2,2) *P* = 0.010 Non-psychotic Group F 0.5 (df 1,18) *P* = NS Time F 4.4 (df 2,36) *P* = 0.020 Interaction F 2.3 (df 2,2) *P* = NS Psychotic Group F 9.8 (df 1,16) *P* = 0.006 *Quality of Life* Overall Group F 1.8 (df 1,36) *P* = NS Time F 12.5 (df 2,72) *P* = 0.000 Interaction F 4.6 (df 2,2) *P* = 0.010 Non-psychotic Group F 0.5 (df 1,18) *P* = NS Time F 4.4 (df 2,36) *P* = 0.020 Interaction F 2.3 (df 2,2) *P* = NS Psychotic Group F 9.8 (df 1,16) *P* = 0.006 Scale Global Assessment of Function Scale

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Intervention G1: ECT G2: rTMS G3: G4: ECT Psychotic vs none G5: rTMS Psychotic vs none Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11 Baseline score, mean (SD) G1: 31.0 (8.5) G2: 34.1 (11.7) G3: Intervention4: 29.0 (7.0) vs. 33.0 (9.8) G5: 28.9 (9.9) vs. 38.3 (11.8) Endpoint score, mean (SD) G1: Awk2 46.8 (17.2)/ endpoint 61.5 (21.5) G2: Awk2 44.5 (14.7)/ endpoint 51.0 (18.2) G3: G4: Awk2 50.6 (18.3)/ endpoint 65.5 (18.8) vs. Awk2 43.0 (16.0)/ endpoint 57.5 (24.2)

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G5: Awk2 36.1 (8.2)/ endpoint 39.4 (14.5.) vs. Awk2 51.4 (15.5)/ endpoint 60.5 Change, mean (SD) G1: Awk2 15.8/endpoint 30.5 G2: Awk2 10.4/endpoint 16.9 G3: G4: Awk2 21.6/endpoint 36.5 vs. Awk2 10.0/endpoint 24.5 G5: Awk2 7.2/endpoint 10.5 vs. Awk2 13.1/endpoint 22.2 Other Overall Group F 0.7 (df 1,38) *P* = NS Time F 40.8 (df 2,76) *P* = 0.000 Interaction F 3.4 (df 2,2) *P* = 0.040 Non-psychotic Group F 1.0 (df 1,19) *P* = NS Time F 19.8 (df 2,38) *P* = 0.000 Interaction F 0.3 (df 2,2) *P* = NS Psychotic Group F 8.2 (df 1,17) *P* = 0.01

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adverse Events NR 5 rTMS patients had mild headaches *Neuropsychological or executive functioning* Measures, Results MMS. (ECT baseline 25.9 (4.1), ECT end of treatment 24.5 (7.6); rTMS baseline 24.8 (4.1), rTMS end of treatment 26.3 (3.9), repeated measures ANOVA [group effect $F(1,29) = 0.1$, P = NS; time effect $F(2,58) = 1.3$, P = NS; interaction $F(2,2) = 2.3$, P = NS) analysis was also performed forpsychotic–nonpsychotic groups with similar results. Predefined No *MMSE* Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 25.9 (4.1) G2: 24.8 (4.1)

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Endpoint score, mean (SD) G1: 24.5 (7.6) G2: 26.3 (3.9) Change, mean (SD) G1: -1.4 G2: +1.5 Other ANOVA [group effect F(1,29) = 0.1, *P* = NS; time effect F(2,58) = 1.3, *P* = NS; interaction F(2,2) = 2.3, *P* = NS) analysis was also performed forpsychotic–nonpsychotic groups with similar results. Adequate information *Attrition* Overall, % 0% At end of treatment, % 0 At end of followup, % 0 Withdrawals due to efficacy, % 0

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to adverse events, % 0 *Adherence/ compliance* Compliance All patients completed study
Author, Year Dannon, 2002[45] *Country, setting* Israel; medical center outpatient program *Funding* National Association for Research in Schizophrenia and Affective Disorders NARSAD) and Stanley Research Foundation *Research Objective* To compare longitudinal outcomes of patients who responded to either rTMS or ECT *Quality Rating* Fair	*Study design* Observational *Type of analysis* Study references Grunhaus 2000 (Refid #368) which is open study of 40 patients - suspect this is continuation of this with additional patients. Of 43 responders initially identified, 2 are excluded *N* 43 *Duration* 3 month and 6 month follow-up; Primary outcome was presence or absence of relapse at 3 or 6 months. Relapse defined as return of depressive symptomatology meeting DSM-IV criteria	*TRD definition* • Not required or not specified to be in current episode *Setting(s)* Outpatient *Inclusion criteria* • Responded to treatment with either ECT or rTMS • over age 18 years • DSM-IV diagnosis of MDD with or without psychotic features • no personal or first-degree family history of seizure • no major medical, neurologic, or neurosugical disorder. • Response for inclusion defined as HAM-D17 <= 10 or demonstrating 60% drop in HAM-D and final global	*Subgroups* No sub-group analysis of psychosis although permitted in study *Treatment Failure* Patients referred for ECT because of nonresponse or psychotic MDD Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR	*HAM-D 17* Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 7.90 (4.54) G2: 7.75 (3.74) Endpoint score, mean (SD) At 3 months G1: 7.71 (5.03) G2: 6.40 (4.91) At 6 months G1: 8.40 (5.60) G2: 7.90 (7.14) Change, mean (SD) At 3 months G1: -0.01 G2: 1.35 At 6 months G1: -0.5 G2: -0.15	*Quality of Life* Global Assessment of Functioning (GAF), or GAS Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 71.81 (10.39) G2: 72.50 (9.39) Endpoint score, mean (SD) At 3 months G1: 75.52 (13.81) G2: 79.75 (12.92) At 6 months G1: 72.8 (11.94) G2: 77.75 (17.13) Change, mean (SD) At 3 months G1: -3.71 G2: -7.25

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	for MDD with a HAM-D17 score of >= 16 points *Interventions* A - Electroconvulsive Therapy (ECT)B - Repetetive Transcranial Magnetic Stimulation (rTMS) G1: ECT G2: rTMS Antidepressants prescribed at end of ECT and rTMS for all patients *Parameters* rTMS: Location = Left Dorsolateral Prefrontal Cortex Frequency = 10Hz Intensity = 90% MT Per Session = 6 sec trains with 30 sec interval in between at 20 times. Number of sessions = daily for 20 days ECT Methods: Location: Initially unilateral; switched to bilateral txt after 6th txt if HRSD had not decreased by >= 30% Threshold = 2.5 times threshold energy to maintain a seizure	assessment scale (GAS) >=60 *Exclusion criteria* NR in this article - but Grunhaus 2000 (Refid #368) reports that patients with additional axis-I diagnoses were excluded from the study	Previous treatment, not specified, % G1: NR G2: NR *Polarity, %* Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR Bipolar II G1: NR G2: NR *Age, mean yrs* G1: 57.43 G2: 56.85 *Sex, % females* G1: 70% G2: 66.7% Note: there might be a typo in table in reporting gender ratio, percentage reported here is based on numbers in"rTMS" column in paper because they add up to correct n for "ECT column."	Responders, n NR Remitters, n NR Relapse (HAM-D ≥ 16) At 3 months G1: 2 G2: 1 At 6 months G1: 2 G2: 3 Combined G1: 4 G2: 4 Other HAM-D17 3 mos = *P* = NS, CI -1.83, 4.46; 6 mos = *P* = NS, CI -3.61, 4.61 ECT vs. rTMS *BDI* NR *MADRS* NR *IDS* NR *CGI-S* NR *CGI-I* No	At 6 months G1: -0.99 G2: -5.25 Other 3 mos *P* = NS, CI -12.69, 4.23; 6 mos *P* = NS, CI -14.40, 4.50 *Adverse Events* NR *Neuropsychological or executive functioning* No Measures, Results NR Predefined NA - No AE data reported *MMSE* NR *Attrition* Overall, % 4.6% At end of treatment, % NR At end of followup, % G1: 0 G2: 9

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	length of >= 25 sec. Number of sessions = NR *Strategy* There is no description of whether participats were taking medications prior to treatment with ECT or rTMS. Co-medications were not allowed during period when ECT or rTMS was given with exception of lorazepam. Antidepressants		*Race, % white* G1: NR G2: NR *Right handed, %* G1: NR G2: NR Groups similar at baseline No- what are differences All P values were reported as non-significant for baseline characteristics, however following characteristics showed some variation between groups: Duration of episode (months) (mean +/- SD), ECT grou*P* = 6.71 +/- 7.56, rTMS gr *Tier* Tier 3 only mention of whether participants failed any previous treatments is in Grunhaus (#368).	NR Baseline n NR Endpoint score, mean (SD) NR Achieving 1 or 2 score, %(SD) NR Other NR *Other*	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: NR G2: NR Other • 43 people agreed to be part of study, two were dropped before final analysis, no explanation is given, and they are not included in final analysis. • The Michigan Adequacy of Treatments (MATS) was also included in this study. MATS for ECT was 3 mos FU 1.92 (1.04 SD), 6 mos FU 1.82 (0.98 SD); rTMS 3 mos FU 2.28 (1.07 SD), 6mos 2.44 (1.03 SD). CI for 3 mos FU ECT vs. rTMS is -1.14 - 0.43, *P* = N *Adherence/ compliance* NR

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Rosa et al, 2006[2] *Country, setting* Brazil, university clinic, inpatients and outpatients included *Funding* Not reported *Research Objective* To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Included completers analysis & ITT (LOCF), ITT is reported in abstraction *N* 42 *Duration* Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk *Interventions* G1: ECT G2: rTMS *Medications allowed* ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed *Strategy* Switch	*TRD definition* • A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) • Not required or not specified to be in current episode *Tier 1 Inclusion criteria* • Age 18-65 • unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms *Exclusion criteria* • History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease • Use of cardiac pacemaker • Pregnancy	*Treatment Failure* Previous treatment, not specified, % Overall:100% *Polarity, %* Unipolar Overal: 100% *Age, mean yrs* G1: 46.0 G2: 41.8 *Sex, % females* G1: 46.7 G2: 60.0 *Race, % white* G1: 80.0 G2: 90.0 *HAM-D 17* Baseline n G1: 20 G2: 22 Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20]	*HAM-D 17* Endpoint score, mean (SD) NR (graph only) Change, mean (SD) NR (graph only) *P* = 0.86 Responders, n (%) G1: 6 (20) G2: 10 (45) *P* = 0.35 Remitters, n (%) Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) *P* = 0.65 Instrument CGI Endpoint score, mean (SD) 2wk G1: 4.0 (1.0) G2: 3.7 (1.1) 4wk G1: 3.2 (1.5) G2: 3.1 (1.3) Change, mean (SD) NR, *P* = 0.672	*Quality of Life* NR *Adverse Events* Overall, % NR Suicidality, % G1: 10.0 G2: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study *Neuropsychological or executive functioning* NS differences between groups on all neuropsychological tests following wk2 & wk4. (Weschler Adult Intelligence Scale - R subtests (Vocabulary, Cube) Wechsler Memory Scale subtest (Digit Span) Rivermead Behavioral Memory Test)

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS: • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks ECT: • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5)		*CGI* Baseline n G1: 20 (N analyzed =15) G2: 22 (N analyzed =20) Baseline score, mean (SD) G1: 4.7 (0.8) G2: 4.3 (0.8)		*MMSE* NR *Other* *Attrition* Overall, % 16.7 At end of treatment, % G1: 15.0* G2: 9.1* *Prior to completing txt (txt end date differed by pt) At end of follow-up, % G1: 25.0 G2: 9.1 Withdrawals due to efficacy, % G1: NR G2: 0.0 Withdrawals due to adverse events, % G1: NR G2: 9.1 Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy *Adherence/ compliance* NR

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Schulze-Rauschenbach et al., 2005[63] *Country, setting* Germany, Psychiatric University Hospital, inpatients *Funding* NR *Research Objective* To compareneurocognitive effects of unilateral ECT and rTMS using a control *Quality Rating* Fair	*Study design* Observational *Type of analysis* Observational study of patients completing txt *N* 30 *Duration* Not clear- testing took place 8.8 days on average afterlast treatment Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks. *Interventions* Control G1: ECT G2: rTMS *Medications Allowed* Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study *Parameters* ECT:	*TRD definition* • Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Consecutively admitted patients with DSM–IV diagnosis of MDD • Age over 18 years *Exclusion criteria* • Previous treatment with ECT or rTMS • Additional Axis I diagnosis	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 46.7 G2: 47.7 *Sex, % females* G1: 50 G2: 44 *HAM-D 17* Baseline n G1: 14 G2: 16 Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5) *BDI* Baseline n G1: 14 G2: 16 *SSMQ* Baseline n G1: 14 G2: 16 Baseline score, mean (SD)	*HAM-D 17* Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9) Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, *P* = NS Responders, n G1: 6 (46%) G2: 7 (44%) *P* = 0.90 *BDI* Change, mean (SD) G1: 7.6 G2: 6.4Group x time, *P* = NS *SSMQ* Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8) Change, mean (SD) G1: 5.5 G2: 20.6	*Quality of Life* NR *Adverse Events* One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included. *Neuropsychological or executive functioning* Test scores • ECT Pre / Post vs. rTMS Pre / Post Post; *P* = Post Ect vs. Post rTMS • Learning and anterograde memory AVLT • Immediate recall (trials 1-5); *P* = NS • Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); *P* < 0.01 • Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); *P* < 0.05 • Recognition hits; *P* = NS and Recognition

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) rTMS • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: 400-600 • Total number of sessions: 2-3/wk *Strategy* Augment or add-on		G1: -20.7 (19.0) G2: -16.8 (16.9)		false alarms; *P* = NS MPT • Recall trial; *P* = NS and Delayed recall; *P* = NS Retrograde memory Retrograde AVLT • Recall; *P* = NS and Recognition hits; *P* = NS • Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); *P* < 0.05 Four-card task • Free recall 0.4 (0.5) vs. 1.4 / (1.2); *P* < 0.05 • Recognition; *P* = NS • AMI Recall score; *P* = NS Subjective memory • SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); *P* < 0.05 Other cognitive functions • MMSE; *P* = NS, TrailMakingTest A; *P* = NS, TrailMakingTest B; *P* = NS, Digit span (WAIS-R); *P* = NS, Letter-number span;

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					P = NS, Word fluency (LPS); *P* = NS *MMSE* G1: ECT G2: rTMS G3: Control Baseline n G1: 14 G2: 16 G3: 15 Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0) Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1) Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01 Other *P* = NS *Attrition* Overall, % 3.3 At end of treatment, % G1: 7

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G2: 0 At end of follow-up, % G1: NR G2: NR Withdrawals due to efficacy, % G1: 0 G2: 0 Withdrawals due to adverse events, % G1: 7 G2: 0 One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included inanalysis *Adherence/ compliance* NR

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] *Country, setting* USA, Single center, University department of psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint *Interventions* G1: High-left TMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous TMS exposure • Bipolar disorder • Previous failure of nine or more bitemporal ECT treatments • Current major depressive episode longer than 5 years • History of substance abuse or dependence withinpast 2 years, • Antisocial or borderline personality disorder,	*Subgroups* Pain, subgroup analysis presented in Avery et al, 2007[11] *Baseline n* G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 44.3 G2: 44.2 *Sex, % females* G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR	*HAM-D 17* Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time *P* = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) *P* = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) *P* = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) *BDI* Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed significant group by time interaction (*P* = 0.003)	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, *P* < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• Active suicidal ideation • Vurrent symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • Any other major psychiatric or medical comorbidity	Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)		*Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$) no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures., There was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session. *MMSE* NR

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % 7.4% (5/68) At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued *Adherence/ compliance* NR
Author, Year Holtzheimer et al., 2004[19] *Country, setting* USA, single center, outpatient/inpatient status not clearly stated *Funding* University of Washington	*Study design* RCT *Type of analysis* ITT *N* 15 *Duration* Primary endoint following 2 weeks of treatment and follow-up 1 week after txt	*TRD definition* • Subjects must have failed at least 2 previous antidepressant trials due to lack of response to adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in current episode	*Treatment Failure* Failed 7 or more, % G1: 85.7 G2: 37.5 *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 40.4 G2: 45.4	*HAM-D 17* Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7) At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)	*Quality of Life* NR *Adverse Events* No major adverse events at any point in study. Some subjects experienced mild pain withactive rTMS, but treatments were generally well tolerated.

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable *Quality Rating* Fair	completed *Interventions* G1: rTMS G2: Sham *Medications Allowed* All pts discontinued (failed) AD medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5 • Inter-train interval: 30-60 • Pulses per session: 1600 • Total number of sessions: 10 over 2 wks Sham rTMS • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp	*Tier 1* *Inclusion criteria* • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18 *Exclusion criteria* • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy	*Sex, % females* G1: 57.1 G2: 42.9 *Right handed, %* G1: 100 G2: 100 *HAM-D 17* Baseline n G1: 7 G2: 8 Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3) *BDI* Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)	1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8 At week 2 G1: 8.1 G2: 5.5 1 week follow-up G1: 3.9 G2: 3.2 All endpoints, *P* = NS Responders, n (%) At week 1 G1: 0 G2: 0 At week 2 G1: 2 (28.6) G2: 1 (12.5) 1 week follow-up G1: 0 G2: 0 *BDI* Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)	*Neuropsychological or executive functioning* Both groups performed equally well withexception of one measure of verbal memory, Trial 7 ofRey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); *P* < 0.05). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions. *MMSE* NR There were no major adverse events at any point instudy. Some subjects experienced mild pain withactive rTMS, but treatments were generally well tolerated.

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4) 1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9) Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1 Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), *P* = NS	*Attrition* Overall, % 0 during treatment. 3 (20%) beforefinal assessment at week 3 At end of treatment, % 0 At end of follow-up, % G1: 28.6 G2: 12.5 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR *Adherence/ compliance* Compliance All 15 subjects completed all 10 txt sessions
Author, Year Padberg et al., 1999[21] *Country, setting* Germany, university clinic, patient status not clear	*Study design* RCT *Type of analysis* ITT *N* 18	*TRD definition* • 2+ failed txt trials of 4+ wks duration including at least 1 tricyclic • Required to be in current episode	*Treatment Failure* Current episode failures, mean G1: 4.0 (2.2) G2: 3.2 (0.8) G3: 3.2 (1.2)	*HAM-D 21* Endpoint score, mean (SD) G1: 28.5 (9.4) G2: 21.5 (21.5) G3: 23.5 (10.4)	*Quality of Life* NR *Adverse Events* Headache, % G1: 16.7 G2: 16.7 G3: NR

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Funding Magstim Company Ltd. & Micromed Medizin-Elektronik GmbH *Research Objective* Compare antridepressant efficacy and tolerability of fast, slow, and sham rTMS in TRD *Quality Rating* Fair	*Duration* 1 week of active txt Primary outcome: Change in HAM-D after 5 txt sessions *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: Fast rTMS G2: SlowrTMS G3: Sham rTMS *Medication allowed* 83.3% of pts continued on their current [failed] AD medication,others were not on a med and did not start one prior to trial *Strategy* Augmentation *Parameters* rTMS High • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 5 • Length of train (seconds): 5 • Inter-train interval: 30 • Pulses per session: 250	*Tier 1* *Inclusion criteria* MDD (DSM IV) *Exclusion criteria* Organic brain disorders, contraindications for rTMS	*Polarity, %* Unipolar 100 *Age, mean yrs* G1: 63.5 G2: 46.7 G3: 43.3 *Sex, % females* G1: 33.3 G2: 83.3 G3: 66.7 *Right handed, %* G1: 100 G2: 100 G3: 100 *HAM-D 21* Baseline n G1: 6 G2: 6 G3: 6 Baseline score, mean (SD) G1: 30.2 (9.5) G2: 26.7 (9.4) G3: 22.2 (8.8) *MADRS* Baseline n G1: 6 G2: 6 G3: 6	Change, mean (SD) G1: -1.7 G2: -5.2 G3: -1.3 $P > 0.05$ Responders, n NR Remitters, n NR *MADRS* Endpoint score, mean (SD) graph only Group x time, $P < 0.1$	Focal Pain at rTMS site during stimulations, %: G1: 50 G2: 33.3 G3: 0 There were no serious AE. *Neuropsychological or executive functioning* Verbal Memory Tests (included 3 learning trials and a consecutive, delayed recall task after distraction): Verbal memory performance improved significantly after fast rTMS Learning 1. $P = 0.006$ 2. NA 3. Fast rTMS improvement $P = 0.032$, Slow rTMS P = NS, Sham decrease in performance $P = 0.09$ *MMSE* NR

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions: 5/wk rTMS Low • Frequency (Hz):0.3 • Motor threshold (%): 90 • Number of trains: 10 • Length of train (seconds): 25 • Inter-train interval: NR • Pulses per session: 75 • Total number of sessions: 5/wk Sham: • Same as high rTMS except coil angled at 90 degrees with 1 wing resting on skull		Baseline score, mean (SD) graph only		*Attrition* Overall, % NR, "no pts asked for discontinuation of rTMS" At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR - "compliance was excellent"

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Fitzgerald et al., 2003[15] *Country, setting* Australia 2 general psychiatric services, outpatients *Funding* National Health and Medical Research Council and a grant fromStanley Medical Research Institute *Research Objective* To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 60 *Tier 1* *Duration* Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt. *Interventions* G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham *Medications Allowed* 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics	*TRD definition* • Failed a minimum of 2 courses of antidepressant medications (6+ weeks) Not required or not specified to be in current episode *Inclusion criteria* • DSM-IV diagnosis of Major Depression (included bipolar depression) *Exclusion criteria* • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders	*Treatment Failure* Mean failed trials Overall (SD) 5.68 (3.40) Polarity, % Bipolar I G1: 5 G2: 5 G3: 20 *Age, mean yrs* G1: 42.2 G2: 45.55 G3: 49.15 *Sex, % females* G1: 40 G2: 35 G3: 55 *Right handed, %* G1: 90 G2: 100 G3: 85 *BDI* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)	*BDI* Endpoint score, mean (SD) At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7) Change, mean (SD) At 2 weeks G1:- 6.4 G2: -7.8 G3: -2.3 *P* = 0.03 *MADRS* Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5) Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) *P* = 0.004 G1: vs. G3, G2 vs. G3, *P* < 0.005 Responders, n 20% ≤ decrease	*Quality of Life* GAF Global Assessment of Functioning Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15) Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8) Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Quality of Life* Overall group

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Augmentation *Parameters* rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week		*MADRS* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)	At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) *P* = 0.07 Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 *P* = NR *CGI* Endpoint score, mean (SD) NR *P* =.01	F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Adverse Events* Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. • Although there was no difference in incidence of these adverse effects (*P* =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					• Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: • One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium *Neuropsychological or executive functioning* • No deterioration in performance was found in any cognitive • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on verbal paired associates (t50=−7.3;

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					P < 0.001), verbal fluency (t48=−3.8; *P* < 0.001), and digit span forwards (t48=−1.8; *P* = 0.003) subscales;Personal Semantic Memory Schedule (t50=−2.4; *P* = 0.02); andAutobiographical Memory Schedule (t50=−1.9; *P* = 0.05). • A similar pattern of improvements was seen for each of • treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across sametimes. *MMSE* NR *Other* *Attrition* Overall, % None in initial 2 week treatment phase

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of treatment, % 0 At end of follow-up, % NR But at least 28.3% did not continue on through 2nd 2 weeks Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear *Adherence/ compliance* NR

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Manes et al., 2001[29] Includes additional neuro-psychological outcomes reported in Moser et al., 200230 *Country, setting* US, outpatient clinic *Funding* NIMH *Research Objective* To examineantidepressant efficacy of rTMS in a TRD population *Quality Rating* Fair	*Study design* RCT *Type of analysis* cannot tell if ITT *N* 20 *Duration* 2 weeks (1 week of treatment, 1 wk follow-up following last treatment) Primary outcomes HAM-D at end of treatment and at 1 week follow-up *Interventions* G1: rTMS (N=10) G2: Sham rTMS (N=10) *Medications allowed* No antidepressant medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20	*TRD definition* • Not required or not specified to be in current episode *Setting(s)* Outpatient Psychiatric *Inclusion criteria* • Major/Minor Depression (DSM IV), • TRD (1+ failed trial) *Exclusion criteria* NR	*Subgroups* Age 50+ *Treatment Failure* Mean failed trials G1: 4 (2.3) G2: 4 (1.2) *Polarity, %* Major Depression G1: 80 G2: 100 Dysthymia G1: 20 G2: 0 *Age, mean yrs* G1: 60.5 G2: 60.9 *Sex, % females* G1: 50 G2: 50 *Race, % white* G1: 100 G2: 100 *HAM-D* Baseline n G1: 10 G2: 10	*HAM-D* Endpoint score, mean (SD) At 1 week G1: 13.7 (5.4) G2: 16.2 (8.5) 1 week Follow-up G1: 14.4 (6.4) G2: 15.5 (9.1) Change, mean (SD) At week 1 G1: -9 G2: -6.5 1 week follow-up G1: -8.3 G2: -7.2 All time points *P* >0.66; pts with MDD only - *P* = 0.3919 Responders, n (%) G1: 3 (30) G2: 3 (30) *P* = NS Remitters, n G1: 2 G2: 2 *P* = NR	*Quality of Life* NR *Adverse Events* Headache, % G1: 40% G2: 0% Other: Local pain/local discomfort: 10%/40% vs. 0%/40%; anxiety: 0 vs 10% *Neuropsychological or executive functioning* **30 (endpoint: mean of 3 days after 5 days of txt) Trail Making Test B score Baseline: rTMS: 87.22 Sham: 103.67 Follow-up rTMS: 58.59 Sham: 100.64 **some variation in pts included in two samples but reported as same study by authors. #1564 includes at least 1 participant <50 years old, n=19

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk Sham: • Same stimulation, figure 8 coil was above top of skull and handle was placed against head		Baseline score, mean (SD) G1: 22.7 (5.2) G2: 22.7 (7.1)		Other neuropsychological tests showing no statistical significance in either group: Trail Making Test-A, Stroop Test, WAIS-R digit symbol, Controlled Oral Word Association, Boston naming test, stentance repitition, Rey Auditory Verbal Learning test, & Judgement of Line Orientation *MMSE* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 28.7 (1.4) G2: 28.6 (1.3) Endpoint score, mean (SD) At Week 1 G1: 29.6(0.7)) G2: 29.3 (0.7) At Follow-up Week 1 G1: 29.6(1.8) G2: 29.2 (0.8) Change, mean (SD) NR

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					1. *P* >0.41 2. *P* = NA 3. *P* = NR *Attrition* NR *Adherence/ compliance* NR

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year McLoughlin et al., 20077 Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating major depressive	*Study design* RCT- pragmatic and single blinded (raters) *Type of analysis* m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months *Interventions* G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) *Polarity, %* MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % *Age, mean yrs* G1: 63.6 G2: 68.3 *Sex, % females* G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93 Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End ot treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
episodes in patients referred for ECT *Quality Rating* Good	*Strategy* Augmentation *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5		*BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25 Responders, n NR Remitters, n NR	suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR *Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					(verbal fluency, anterograde memory, and retrograde memory) *MMSE* *Baseline n* G1: 16 G2: 22 Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR
Author, Year O'Connor, 2003[64] *Country, setting* United States, University Hospital, inpatient vs. outpatient population not clearly reported *Funding* NIH/NIMH and a NARSAD grant	*Study design* Observational *Type of analysis* Completers *N* 28 *Duration* • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks).	*TRD definition* • Patients referred for ECT • AD failures not required *Tier 3* *Inclusion criteria* • Met criteria for MDD • HRSD > 18 *Exclusion criteria* • Psychosis, acute suicidality, other	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD *Age, mean yrs* G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2	*HAM-D* Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5) Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time $P < 0.01$	*Quality of Life* *Adverse Events* NR *Neuropsychological or executive functioning* Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning) Baseline n G1: 14 G2: 14

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition *Quality Rating* Fair	• Patients assessed for follow-up 2 weeks post txt *Medications allowed* rTMS patients completed a washout of all psychotropic medications while ECT continued all medications *Strategy* Switch strategy for rTMS and augment or add-on strategy for ECT group *Interventions* G1: ECT G2: rTMS *Parameters* ECT • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12, 3/wk rTMS • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8	current Axis I diagnoses in DSM IV • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent	*HAM-D* Baseline n Completers G1: 14 G2: 14 Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) *P* = 0.001 *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)	Responders, n G1: NR G2: 0 Remitters, n G1: NR G2: 100% *Other* Validated measure Yes *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83) Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with2 week follow-up results (*P* > 0.05)	Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09) Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00) Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: *P* > 0.05 G2: 44.07 (10.43) RAVLT, Acquisition, mean (SD) Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09). End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) *P* < 0.01. Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) *P* > 0.05.

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks			No significant interaction between treatment sessions and groups with respect to LN (*P* > 0.05)	RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD) Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08) End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80) Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07). Transient News Events Test (TNET-measure of retrograde memory) Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12) Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33) Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12)

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$. Cognitive function/memory impairment reported as primary outcome measures. *MMSE* NR *Attrition* Overall, % No attrition At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] *Country, setting* USA, Single center, University department of psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint *Interventions* G1: High-left TMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence withinpast 2 years,	*Subgroups* Pain, subgroup analysis presented in Avery et al, 200711 *Baseline n* G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 44.3 G2: 44.2 *Sex, % females* G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR	*HAM-D 17* Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time *P* = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) *P* = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) *P* = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) *BDI* Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, *P* < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity	Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)	Random Regression analyses revealed significant group by time interaction (P = 0.003)	*Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% (P < 0.05) no statistically significant (P > 0.05) time by treatment group interactions for any of neuropsychological test measures.There was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant (P > 0.05) differences between groups for any session. *MMSE* NR

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

					Attrition Overall, % 7.4% (5/68) At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued *Adherence/ compliance* NR
Author, Year Bretlau, 2008[41] *Country, setting* Denmark, setting NR, outpatients *Funding* Commercial source-please list name.supported by Medicon Valley Academy and an unrestricted research grant from H Lundbeck A/S	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 49 *Duration* 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. Escitalopram was adminitered during the entire trial at 20mg	*TRD definition Required to be in current episode* Yes *Setting(s)* Not clearly reported *Inclusion criteria* • Aged 18 - 75 years; • meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); • failed to respond to at least one previous	*Subgroups* No sub-group analysis *Treatment Failure* Failed 1 or more, % G1: 100 G2: 100 *Failed 2 or more, %* G1: NR G2: NR Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9)	*HAM-D* Yes HAM-D 17 Other, please describe.HAM-D 6 G1: rTMS + escitalopram G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22	*Quality of Life* NR *Adverse Events* Overall NR Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00 Cardiovascular adverse events, % G1: palpatations: 3wk/ 12 wk mean: 0.23/0.14

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

Research Objective To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment phase. *Quality Rating* Fair	daily (10 mg daily for first wk of trial). Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals. *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n= 24) G1: rTMS + escitalopram G2: sham TMS + escitalopram G1: rTMS + escitalopram** G2: sham TMS + escitalopram** *Parameters* • Location = Left Dorslateral prefrontal cortex • Frequency = 8 Hz • Intensity = 90% motor threshold • Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. • Number of sessions = 15	adequate (at least 6 weeks) antidepressant treatment during the current episode; • subjects with heart disorders or diabetes were included if they were in a somatically stable phase *Exclusion criteria* • Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders; • potential risk factors for escitalopram such as hypersensitivity to the Intervention, • intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, • pregnancy or insufficient contraception in females of reproductive age; • risk factors for TMS such as history of epilepsy, • metal implants in the head or neck regions, • pacemaker or other electronic implants, • receiving antipsychotics; • having major suicide ideation.	Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR Bipolar II G1: NR G2: NR *Patient Characteristics* *Age, mean yrs* G1: 53.1 G2: 57.8 *Sex, % females* G1: 68% G2: 57% *Race, % white* G1: NR G2: NR *Not Specified, %* G1: NR G2: NR *Right handed, %* G1: NR G2: NR Groups similar at baseline Yes *Tier*	Baseline score, mean (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5) Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1), Awk3 = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2) Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2 Responders, n G1: NR G2: NR	G2: 0.30/0.12 Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22 Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06 Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39 Somnolence, % NR Suicidality, % NR Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (P <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

	Strategy Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment		Tier 22A: 1+ failed, MDD	Remitters, n G1: NR G2: NR Other The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favour of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.83 (0.22-1.44), P = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.78 (0.18 - 1.39), P = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.48(-0.12 - 1.07), P = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.64 (0.04 - 1.24), P = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.47 (-0.11 - 1.07), P = 0.22; HAM-D6 Awk 2 Effect size (95% CI) and	events inlcude: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				Mann-Whitney P: 0.73 (.018 -1.39), P = 0.05; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.80 (0.20 - 1.42), P = 0.01; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.09 -1.29), P = 0.02; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney P:0.50 (-0.10 -1.09), P = 0.10; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.0.50 (-0.10 - 1.09), P = 0.09; BDI G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0) Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7),	= 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); *Neuropsychological or executive functioning* No Measures, Results NR Predefined Yes MMSE No NR Baseline n NR Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) NR Other *Other* Yes Study utilized the UKU scale as listed before - Other adverse events inlcude:

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9) Change, mean (SD) G1: 12.4 G2: 9.4 Responders, n NR Remitters, n NR Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.73 (0.12 - 1.33), P = 0.03; Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.84 (0.24 -1.46), P = 0.00; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.64(0.02 -1.22), P = 0.03; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.04 - 1.24), P = 0.03; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.46 (-0.12 - 1.06), P	tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				= 0.12; *MADRS* NR *IDS* NR *CGI-S* NR CGI-I NR Instrument Major Depression Inventory (MDI) Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6) Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7) G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8)	12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); Adequate information Yes *Attrition* Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out. At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0 At end of follow-up, % G1: 21% G2: 4% Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				Change, mean (SD) G1: 17.4 G2: 14.4 MDI Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.36 (-0.23 - 0.94), P = 0.18; Awk 3 Effect size (95% CI) and Mann-Whitney P:0.43 (-0.16 - 1.03), P = 0.29; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.29 (-0.29 - 0.88), P =0.20; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.22 (-0.36 - 0.81), P = 0.72; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.23 (-0.36 -0.81), P = 0.43;	

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Rush et al., 2005[24], *Country, setting* US, multicenter, outpatient psychiatric *Funding* Cyberonics, Inc. *Research Objective* To compare adjunctive VNS to sham in TRD patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* m-ITT/P*P* for efficacy, ITT for Aes *N* 235 *Duration* 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt *Interventions* G1: VNS G2: Sham *Medications allowed* pts allowed up to 5 antidepressants, mood stablizers, or other psychotropic medications *Strategy* Augmentation *Parameters* VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs	*TRD definition* • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode *Tier 1* *Inclusion criteria* • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium *Exclusion criteria* • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disoder, suicidality • risks related to surgical implantation	*Treatment Failure* Percent with 4-6 current episode failures G1: 46.5% G2: 40.0% *Polarity, %* Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6 Bipolar II G1: 6.3 G2: 5.5 *Age, mean yrs* G1: 47.0 G2: 45.9 *Sex, % females* G1: 59 G2: 66 *Race, % white* G1: 97 G2: 96 *HAM-D24* Baseline n G1: 119 G2: 116	*HAM-D24* N analyzed G1: 112 G2: 110 Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) *P* = 0.639 Responders, n G1: 17 (15.2%) G2: 11 (10.0%) *P* = 0.251 *MADRS* Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) *P* = 0.208 Responders, n G1: 17 (15.2) G2: 12 (0.0) *P* = 0.378 *IDS* Endpoint score, mean (SD) NR	*Quality of Life* Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2) Other Physical component between VNS and sham: *P* = 0.480, Mental Component between VNS and sham: *P* = 0.406

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• On/Off cycle parameters: 30 sec on and 5 min off Sham: • Device implanted but not turned on		Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2) MADRS Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3) IDS Baseline n G1: 112 (115 randomized) G2: 110 Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5) CGI-I Baseline n G1: 112 G2: 110	% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) *P* = 0.158 Responders, n G1: 19 (17) G2: 8 (7.3) *P* = 0.032 Remitters, n NR CGI-I Endpoint score, mean (SD) NR Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, *P* = 0.648	*Adverse Events* Overall, % NR Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:– • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%, • hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					patients, were cases of worsening depression requiring hospitalization Cardiac SAEs during implantation: 1.7% v 0% COSTART used to code reported events *Attrition* Overall, % 1.3 (3/235) At end of treatment, % G1: 2.6 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 2.6 G2: 0 9 pts had a protocol violation post randomization *Adherence/ compliance* NR

Evidence Table 19. KQ 4. Adverse Events : Tier 2 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Berman et al., 2000[28] *Country, setting* US, urban community health center, inpatient and outpatients *Funding* Veterans Administration, NIMH, State of CT *Research Objective* To assessefficacy of rTMS in unmedicated TRD patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 20 *Duration* 2 weeks (10 weekdays of txt) Primary outcome = HAM-D at 2wks *Interventions* G1: rTMS G2: Sham TMS *Medications Allowed* All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep *Strategy* Switch *Parameters* rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20	*TRD definition* • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imiprimine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode *Tier 2* *Inclusion criteria* • Current Major depressive episode (via Ham-D) *Exclusion criteria* • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control	*Treatment Failure* Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup) *Polarity, %* Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 *Age, mean yrs* G1: 45.2 G2: 39.4 *Sex, % females* G1: 20 G2: 40 *Race, % white* G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic) *HAM-D 25* Baseline n G1: 10 G2: 10	*HAM-D 25* G1: rTMS G2: Sham TMS Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) *P* < 0.05 Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 *P* = 0.09 Three partial responders symptom severity returned to baseline within 1-2 weeks *BDI* Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) *P* = 0.27	*Quality of Life* NR *Adverse Events* Headache, n G1: 60 G2: 50 Difficulty starting urination great in active group *P* = 0.03 Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) • Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appétit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or

Evidence Table 19. KQ 4. Adverse Events : Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 2 • Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days Sham • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp		Baseline score, mean (SD) G1: 37.1 G2: 37.3		lightheadedness, poor coordination, and muscle stiffness *MMSE* NR *Attrition* Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0 *Adherence/ compliance* NR

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year McLoughlin et al., 2007[7] Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); byGuy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating major depressive	*Study design* RCT- pragmatic and single blinded (raters) Type of analysis m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months *Interventions* G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan) *Strategy* Augmentation	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % *Age, mean yrs* G1: 63.6 G2: 68.3 *Sex, % females* G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93 Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End ot treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
episodes in patients referred for ECT *Quality Rating* Good	*Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5		*BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25 Responders, n NR Remitters, n NR	suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR *Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					(verbal fluency, anterograde memory, and retrograde memory) MMSE Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD) G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects. Attrition Overall to end of treatment 6/46, at 6 months 9/46

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of treatment, % G1: 6/24 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR
Author, Year O'Connor, 2003[64] *Country, setting* United States, University Hospital, inpatient vs. outpatient population not clearly reported *Funding* NIH/NIMH and a NARSAD grant *Research Objective* Two procedures for treating major depressive disorder were compared with regard to their	*Study design* Observational *Type of analysis* Completers *N* 28 *Duration* • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt *Medications allowed*	*TRD definition* • Patients referred for ECT • AD failures not required *Tier 3* *Inclusion criteria* • Met criteria for MDD • HRSD > 18 *Exclusion criteria* • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD *Age, mean yrs* G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2 *HAM-D* Baseline n Completers G1: 14 G2: 14	*HAM-D* Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5) Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time $P < 0.01$ Responders, n G1: NR G2: 0	*Quality of Life* *Adverse Events* NR *Neuropsychological or executive functioning* Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning) Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09)

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
respective effects on mood and cognition *Quality Rating* Poor	rTMS patients completed a washout of all psychotropic medications while ECT continued all medications *Strategy* Switch strategy for rTMS and augment or add-on strategy for ECT group *Interventions* G1: ECT G2: rTMS *Parameters* ECT • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12 rTMS • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600	• known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent	Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) *P* = 0.001 *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)	Remitters, n G1: NR G2: 100% *Other* Validated measure Yes *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83) Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with2 week follow-up results (*P* > 0.05) No significant interaction between treatment sessions and groups with respect to LN (*P* > 0.05)	Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00) Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: *P* > 0.05 G2: 44.07 (10.43) RAVLT, Acquisition, mean (SD) Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09). End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) *P* < 0.01. Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) *P* > 0.05. RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD)

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions:5/wk over 2wks				Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08) End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80) Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07). Transient News Events Test (TNET-measure of retrograde memory) Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12) Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33) Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12) Other Main-effect-of-group (*P* > 0.05). There was evidence of a significant interaction b/t txt grp

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					and txt session: $P < 0.001$. Cognitive function/memory impairment reported as primary outcome measures. MMSE NR *Attrition* Overall, % No attrition At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Schulze-Rauschenbach et al., 2005[63] *Country, setting* Germany, Psychiatric University Hospital, inpatients *Funding* NR *Research Objective* To compare neurocognitive effects of unilateral ECT and rTMS using a control *Quality Rating* Fair	*Study design* Observational *Type of analysis* Observational study of patients completing txt *N* 30 *Duration* Not clear- testing took place 8.8 days on average after last treatment Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks. *Interventions* Control G1: ECT G2: rTMS *Medications Allowed* Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study	*TRD definition* • Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks • Not required or not specified to be in current episode Tier 1 *Inclusion criteria* • Consecutively admitted patients with DSM–IV diagnosis of MDD • Age over 18 years *Exclusion criteria* • Previous treatment with ECT or rTMS • Additional Axis I diagnosis	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 46.7 G2: 47.7 *Sex, % females* G1: 50 G2: 44 HAM-D 17 Baseline n G1: 14 G2: 16 Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5) BDI Baseline n G1: 14 G2: 16 SSMQ Baseline n G1: 14 G2: 16	HAM-D 17 Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9) Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, *P* = NS Responders, n G1: 6 (46%) G2: 7 (44%) *P* = 0.90 BDI Change, mean (SD) G1: 7.6 G2: 6.4Group x time, *P* = NS SSMQ Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8) Change, mean (SD) G1: 5.5 G2: 20.6	*Quality of Life* NR *Adverse Events* One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included. *Neuropsychological or executive functioning* Test scores ECT Pre / Post vs. rTMS Pre / Post Post; *P* = Post Ect vs. Post rTMS Learning and anterograde memory AVLT Immediate recall (trials 1-5); *P* = NS Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); *P* < 0.01 Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); *P* < 0.05 Recognition hits; *P* = NS and false alarms; *P* = NS MPT

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters ECT: • % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) rTMS • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: • Total number of sessions: 2-3/wk *Strategy* Augment or add-on		Baseline score, mean (SD) G1: -20.7 (19.0) G2: -16.8 (16.9)		Recall trial; *P* = NS and Delayed recall; *P* = NS Retrograde memory Retrograde AVLT Recall; *P* = NS and Recognition hits; *P* = NS Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); *P* < 0.05 Four-card task Free recall 2.0 (1.4) / 0.4 (0.5) vs. 1.4 / (1.2); *P* < 0.05 Recognition; *P* = NS AMI Recall score; *P* = NS Subjective memory SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); *P* < 0.05 Other cognitive functions MMSE; *P* = NS, TrailMakingTest A; *P* = NS, TrailMakingTest B; *P* = NS, Digit span (WAIS-R); *P* = NS, Letter-number span; *P* = NS, Word fluency (LPS); *P* = NS MMSE

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G1: ECT G2: rTMS Recognition G3: Control Baseline n G1: 14 G2: 16 G3: 15 Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0) Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1) Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01 Other *P* = NS *Attrition* Overall, % 3.3 At end of treatment, % G1: 7 G2: 0

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of follow-up, % G1: NR G2: NR Withdrawals due to efficacy, % G1: 0 G2: 0 Withdrawals due to adverse events, % G1: 7 G2: 0 One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included inanalysis *Adherence/ compliance* NR

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] *Country, setting* USA, Single center, University, Department of Psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint *Interventions* G1: High-left TMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence Within past 2 years,	*Subgroups* Pain, subgroup analysis presented in Avery et al, 200711 Baseline n G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 44.3 G2: 44.2 *Sex, % females* G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR	HAM-D 17 Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time P = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) P = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) P = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) BDI Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, P < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity	Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)	Random Regression analyses revealed significant group by time interaction (P = 0.003)	*Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS[11]: At 15th session pain TMS 33% vs, sham 3% (P < 0.05) no statistically significant (P > 0.05) time by treatment group interactions for any of neuropsychological test measures.,There was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant (P > 0.05) differences between groups for any session. MMSE NR

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % 7.4% (5/68) At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy,% G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued *Adherence/ compliance* NR
Author, Year Garcia-Toro et al., 2006[17] *Country, setting* Spain, single center, all outpatients *Funding* Fundacio La Marato de TV3	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 30 *Duration* • Primary outcome after 2 weeks of active	*TRD definition* • Failed 2+ txt trials at 4+ weeks • Not required or not specified to be in current episode Tier 1 *Inclusion criteria* • At least 18 yrs old, MDD, unipolar	*Subgroups* None *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100%	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10) At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18) G3: 18.10 (6.15)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in pharmacotherapy

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective To assess the efficacy of high and low frequency rTMS and different locations of activation *Quality Rating* Fair	treatment • Follow-up: 2 weeks post treatment *Interventions* G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam) *Medications allowed* All pts continued (failed) AD medication and other psychotropic meds *Strategy* Augmentation *Parameters* rTMS Low: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session: 1800	*Exclusion criteria* • Contraindications for rTMS and high suicide risk	*Age, mean yrs* G1: 47.2 G2: 48.5 G3: 51.1 *Sex, % females* G1: 70 G2: 40 G3: 40 *Race, % white* NR *Right handed, %* G1: 90% G2: 100% G3: 100% HAM-D 21 Baseline n G1: 10 G2: 10 G3: 10 Baseline score, mean (SD) G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14)	Follow-up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0) Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%) At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), *P* = 0.048 Follow-up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%) G1: vs. G2+G3, *P* = 0.121 Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) *P* = NR	At end of treatment, % G1: 0 G2: 0 G3: 0 At end of follow-up, % NR Does not report which group 3 patients came from Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission computed tomography (20- At end of treatment, % G1: 0 G2: 0 G3: 0 At end of follow-up, % NR Does not report which group 3 patients came from

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions: 10 in 2 wks High • Frequency (Hz):20 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval: 20+5 • Pulses per session: 1200 • Total number of sessions: 10 in 2 wks Sham • Same but with coil angling 45 degrees away from scalp		CGI-S Baseline n G1: 10 G2: 10 G3: 10 Baseline score, mean (SD) G1: 4.7 (0.82) G2: 4.8 (1.0) G3: 4.8 (0.63)	CGI-S Endpoint score, mean (SD) At 2 weeks G1: 4.6 (0.97 G2: 3.8 (1.48) G3: 3.9 (0.99) 2 week follow-up G1: 4.75 (1.16) G2: 4.00 (1.15) G3: 3.7 (1.57)	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission computed tomography (20-Hz rTMS to an area of relatively low activity and 1-Hz rTMS to an area showing relatively high activat *Adherence/ compliance* Compliance all patients completed active 2 week treatment

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Holtzheimer et al., 2004[19] *Country, setting* USA, single center, outpatient/inpatient status not clearly stated *Funding* University of Washington *Research Objective* Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT N 15 *Duration* Primary endoint following 2 weeks of treatment and follow-up 1 week after txt completed *Interventions* G1: rTMS G2: Sham *Medications Allowed* All pts discontinued (failed) AD medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5	*TRD definition* • Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18 *Exclusion criteria* • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy	*Treatment Failure* Failed 7 or more, % G1: 85.7 G2: 37.5 *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 40.4 G2: 45.4 *Sex, % females* G1: 57.1 G2: 42.9 Right handed, % G1: 100 G2: 100 HAM-D 17 Baseline n G1: 7 G2: 8 Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3) BDI Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)	*HAM-D 17* Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7) At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0) 1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8 At week 2 G1: 8.1 G2: 5.5 1 week follow-up G1: 3.9 G2: 3.2 All endpoints, P = NS Responders, n (%) At week 1 G1: 0 G2: 0 At week 2 G1: 2 (28.6) G2: 1 (12.5)	*Quality of Life* NR *Adverse Events* No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally tolerated. *Neuropsychological or executive functioning* Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); $P < 0.05$). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 30-60 Pulses per session: 1600 • Total number of sessions: 10 over 2 wks Sham rTMS • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp			1 week follow-up G1: 0 G2: 0 BDI Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7) At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4) 1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9) Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1 Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), *P* = NS	*MMSE* NR There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated. *Attrition* Overall, % 0 during treatment. 3 (20%) before final assessment at week 3 At end of treatment, % 0 At end of follow-up, % G1: 28.6 G2: 12.5 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adherence/ compliance Compliance All 15 subjects completed all 10 txt sessions

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Boutros et al., 2002[13] *Country, setting* US, Yale School of Medicine and VA-Connecticut, outpatient *Funding* VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer *Research Objective* To provide additional data on efficacy and safety for rTMS as an augment strategy in TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 21 *Duration* 2 weeks txt; follow-up with responders for up to 20 weeks post txt *Interventions* G1: rTMS G2: Sham *Medications Allowed* Pts allowed to continue all current psychotropic meds *Strategy* Augmentation, 3 pts in active and 1 in sham txt were not on any meds *Parameters* rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode Tier 1 Inclusion criteria • Major Depression • HAM-D25 >= 20 Exclusion criteria • Suicidality • "Prominent" psychotic symptoms • History of neurological disorders • Current drug abuse	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 100% *Age, mean yrs* G1: 49.5 G2: 52.0 *Sex, % females* G1: 25 G2: 10 *Right handed, %* G1: 90.9 G2: 88.9 *HAM-D* Baseline n G1: 12 G2: 9 Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)	*HAM-D* Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 *P* = NS Responders, n Defined as 30% improvement on HAM-D G1: 7 G2: 2 Responders, n (%) Defined as 50% improvement on HAM-D G1: 3 G2: 2 *Relapse* Of 6 active treatment responders included in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in the 20-week follow-up, 1 relapsed	*Quality of Life* NR *Adverse Events* Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6 Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR *Attrition* Overall, % 18.2% (4/22) At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10)

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 58 • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp				At end of follow-up, % NR Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR *Adherence/ compliance* NR
Author, Year Fitzgerald et al., 2006[14] *Country, setting* Australia, single center *Funding* Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald)	*Study design* RCT *Type of analysis* ITT (LOCF) *N* 50 *Duration* 2 wks double blind with those with >20% decrease in MADRS to continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary	*TRD definition* • 2+ failed medications with txt duration ≥6 wks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • DSM-IV diagnosis of Major Depressive Episode • MADRS ≥ 20 *Exclusion criteria* • Significant medical illness	*Treatment Failure* Mean failed AD trials (lifetime) G1: 5.6 (3.1) G2: 6.2 (3.0) *Polarity, %* Unipolar G1: 84% G2: 84% *Bipolar* G1: 16% G2: 16% *Age, mean yrs* G1: 46.8 G2: 43.7	*HAM-D 17* Endpoint score, mean (SD) NR Change, % decrease (SD) G1: 45.2% (40.1) G2: 5.4% (23.1) *P* < 0.001 Change, mean G1: -10.17 G2: -1.07 Responders, n (%) At 6wks G1: 13 (52.0) G2: 2 (8.0) *P* = 0.001	*Quality of Life* GAF Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9) Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [*P* <0.05]

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective rTMS versus placebo for depression *Quality Rating* Fair	outcome after 2 and 6 weeks of txt *Interventions* G1: rTMS G2: Sham *Medications allowed* • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, •Antipsychotic medication, • Benzodiazepines *Strategy* Augmentation, 23% not taking medication at study entry *Parameters* rTMS Low Right: Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 3 • Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 *rategy*	• Neurological disorders • Other axis I psychiatric disorders	*Sex, % females* G1: 60 G2: 64 *HAM-D 17* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4) *BDI* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9) *MADRS* Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)*RS* Baseline n	Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0) *P* = NR *BDI* Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7) At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8) At 6 weeks G1: 9.2 (6.7) G2: NR Change, mean (SD) At week 2 G1: 10.9 G2: 7.7 At 4 weeks G1: 18.7 G2: 8.3 At 6 weeks G1: 20.0 G2: NR, *P* = 0.01	Change, mean (SD) G1: 10.2 G2: 1.1 GAF Scale (t=2.0, df=40.2, *P* < 0.05) *Adverse Events* Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved on digit span backward test improved in rTMS only (group by time: *P* = 0.07). Controlled Oral Word Association test improved for both groups (time: *P* = 0.001). Nausea 12% vs. 0, No seizures or manic episodes;

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sequential High Left: • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 • Total number of sessions: 10 sessions 5 days/wk Sham: • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides			Responders, n NR Remitters, n NR *MADRS* Endpoint score, mean (SD) At week 2 G1: 26.2 (10.2) G2: 30.9 (8.2) At week 4 G1: 11.7 (7.1 G2: 34.5 (12.0) At week 6 G1: 8.9 (7.9) G2: NA Change, mean (SD) At week 2 G1: 7.8 G2: 3.2 At week 4 G1: 22.3 G2: 0.4 (increased) At week 6 G1: 25.1 G2: NA	*Neuropsychological or executive functioning* Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction Digit span backward Test Performance improved in rTMS only (group by time: *P* = 0.07). Controlled Oral Word Association Test **I**mproved for both groups *P* = 0.001 *MMSE* NR *Other* Nausea 12% vs. 0 No seizures or manic episodes; *Attrition* Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Group by time, *P* = 0.001 at all time points Responders, n At 6 weeks G1: 11 G2: 2 *P* < 0.05 Remitters, n MADRS < 10 At 6 weeks G1: 9 G2: 0 *P* = 0.005 At week 2 G1: 2 G2: 0 Follow-up at week 3 G1: 3 G2: 0 Follow-up at week 4	After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn At end of treatment, % G1: 0 G2: 12 At end of follow-up, % G1: 56 G2: 100 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Fitzgerald et al., 2003[15] *Country, setting* Australia 2 general psychiatric services, outpatients *Funding* National Health and Medical Research Council and a grant from Stanley Medical Research Institute *Research Objective* To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group *Quality Rating* Good	*Study design* RCT *Type of analysis* ITT *N* 60 *Tier 1* *Duration* Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt. *Interventions* G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham *Medications Allowed* 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics	*TRD definition* • Failed a minimum of 2 courses of antidepressant medications (6+ weeks) Not required or not specified to be in current episode *Inclusion criteria* • DSM-IV diagnosis of Major Depression (included bipolar depression) *Exclusion criteria* • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders	*Treatment Failure* Mean failed trials Overall (SD) 5.68 (3.40) *Polarity, %* Bipolar I G1: 5 G2: 5 G3: 20 *Age, mean yrs* G1: 42.2 G2: 45.55 G3: 49.15 *Sex, % females* G1: 40 G2: 35 G3: 55 *Right handed, %* G1: 90 G2: 100 G3: 85 *BDI* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)	*BDI* Endpoint score, mean (SD) At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7) Change, mean (SD) At 2 weeks G1:- 6.4 G2: -7.8 G3: -2.3 *P* = 0.03 *MADRS* Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5) Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) *P* = 0.004 G1: vs. G3, G2 vs. G3, *P* < 0.005	*Quality of Life* GAF Global Assessment of Functioning Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15) Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8) Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; *P* =.08; LFR-TMS vs. sham: *P* = 0.03; and HFLTMS vs. sham: *P* = 0.09

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Augmentation *Parameters* rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week		*MADRS* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)	Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) *P* = 0.07 Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 *P* = NR *CGI* Endpoint score, mean (SD) NR *P* =.01	*Quality of Life* Overall group F56,2=2.6; *P* =.08; LFR-TMS vs. sham: *P* = 0.03; and HFLTMS vs. sham: *P* = 0.09 *Adverse Events* Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. Although there was no difference in incidence of these adverse effects (*P* =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week				Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium *Neuropsychological or executive functioning* • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					• Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance onverbal paired associates (t50=−7.3; *P* < 0.001), verbal fluency (t48=−3.8; *P* < 0.001), and digit span forwards (t48=−1.8; *P* = 0.003) subscales;Personal Semantic Memory Schedule (t50=−2.4; *P* = 0.02); andAutobiographical Memory Schedule (t50=−1.9; *P* = 0.05). • A similar pattern of improvements was seen for each oftreatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance oncognitive measures did not correlate with changes in MADRS and Beck Depression

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Inventory scores acrosssame times. *MMSE* NR *Other* *Attrition* Overall, % None in initial 2 week treatment phase At end of treatment, % 0 At end of follow-up, % NR But at least 28.3% did not continue on thru2nd 2 weeks Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Su et al., 2005[26] *Country, setting* Taiwan, NS *Funding* Taipei Veterans General Hospital, patient status not reported *Research Objective* To investigate whether two weeks of rTMS applied toLDLPFC can alleviate TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 33 *Duration* 2wk of active txt Primary outcome: HAM-D at 2 weeks (after 10 txt) *Interventions* B - Repetetive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: 20Hz rTMS (N analyzed = 10) G2: 5Hz rTMS (N analyzed = 10) G3: Sham (N analyzed = 10) *Medications allowed* pts allowed to continue all meds constant for 4 weeks prior (e.g. antidepressants, antipsychotics, mood stabilizers, or stimulant	*TRD definition* • TRD (2+ failed adequate trials) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major Depressive Episode or Bipolar (DSV-IV), • Ham-D21 score >=18 *Exclusion criteria* • history of - epilepsy, • any physical and neurological abnormalities, major head trauma, • psychotic symptoms; • current use of a pacemaker, • suicidality	*Subgroups* Ethnicity - Chineese, females by menopausal status *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar G1: 90 G2: 80 G3: 80 Bipolar G1: 10 G2: 20 G3: 20 Bipolar II G1: 10 G2: 10 G3: 10 *Age, mean yrs* G1: 43.6 G2: 43.2 G3: 42.6 *Sex, % females* G1: 70 G2: 80 G3: 70	*HAM-D 17* N analyzed G1: 10 G2: 10 G3: 10 Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 12.3(7.7) G3: 19.0(7.7) Change, mean (SD) At 2 weeks G1: -13.4(4.9) G2: -14.2(6.0) G3: -3.7(9.3) G1: vs. G3, G2 vs. G3 *P* < 0.01 Responders, n G1: 6 (60) G2: 6 (60) G3: 1 (10) G1: + G2 vs. G3 *P* = 0.01 Remitters, n Ham-D17<= 7 G1: 5 (50) G2: 5 (50) G3: 0	*Quality of Life* NR *Adverse Events* Headache, % G1: 20 (n=2) G2: 20 (N=2) G3: 11.1 (N=1) Pain at rTMS site: 16.7% withdrew due to pain at stimulation site SEE AE section *Attrition* Overall, % 9.1 (3/33) At end of treatment, % G1: 0 G2: 16.7 G3: 9.1 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 0 G3: 9.1 Withdrawals due to adverse events, % G1: 0 G2: 16.7 G3: 0

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Augmentation *Parameters* rTMS High: • Frequency (Hz): 20 • Motor threshold (%): 100 • Number of trains:40 • Length of train (seconds):2 • Inter-train interval:28 • Pulses per session: 1600 • Total number of sessions: 5/wk or 10 in 10 weekdays rTMS Low: • Frequency (Hz): 5 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 8 • Inter-train interval: 22 • Pulses per session: 1600 • Total number of sessions:5/wk or 10 in 10 days Sham: • Same as high frequency rTMS. Coil placed at 90 degrees off skull.		*HAM-D 17* Baseline N G1: 10 G2: 12 G3: 11 Baseline score, mean (SD) G1: 23.2 (7.5) G2: 26.5 (5.2) G3: 22.7 (4.7) *BDI* Baseline score, mean (SD) G1: 28.0(9.1) G2: 33.9(7.6) G3: 33.4(9.6) *CGI-S* Baseline score, mean (SD) G1: 4.5(0.7) G2: 4.7(0.8) G3: 4.7(0.48)	*BDI* Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 19.7(12.3) G3: 28.7(15.1) Change, mean (SD) At 2 weeks G1: 15.2(7.5) G2: 14.2(10.4) G3: 4.7(9.1) G1: vs. G3 *P* <0.05 G2 vs. G3 *P* <0.1 *CGI-S* Endpoint score, mean (SD) At week 2 G1: 2.8(1.1) G2: 2.0(0.9) G3: 3.6(1.1) Change, mean (SD) G1: -1.7 G2: -2.0 G3: -1.1 *P* = NS	1 dropped out of sham for worsening of clinical symptoms, this was categorized as LOE *Adherence/ compliance* NR

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Rush et al., 2005[24] Carpenter et al., 2004[25] *Country, setting* US, multicenter, outpatient psychiatric *Funding* Cyberonics, Inc. *Research Objective* To compare adjunctive VNS to sham in TRD patients *Quality Rating* Good	*Study design* RCT *Type of analysis* m-ITT/P*P* for efficacy, ITT for Aes *N* 235 *Duration* 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt *Interventions* G1: VNS G2: Sham *Medications allowed* pts allowed up to 5 antidepressants, mood stabilizers, or other psychotropic medications *Strategy* Augmentation *Parameters* VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs	*TRD definition* • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode *Tier 1* *Inclusion criteria* • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium *Exclusion criteria* • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disoder, suicidality • risks related to surgical implantation	*Treatment Failure* Percent with 4-6 current episode failures G1: 46.5% G2: 40.0% *Polarity, %* Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6 Bipolar II G1: 6.3 G2: 5.5 *Age, mean yrs* G1: 47.0 G2: 45.9 *Sex, % females* G1: 59 G2: 66 *Race, % white* G1: 97 G2: 96 *HAM-D24* Baseline n G1: 119 G2: 116	*HAM-D24* N analyzed G1: 112 G2: 110 Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) *P* = 0.639 Responders, n G1: 17 (15.2%) G2: 11 (10.0%) *P* = 0.251 *MADRS* Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) *P* = 0.208 Responders, n G1: 17 (15.2) G2: 12 (0.0) *P* = 0.378	*Quality of Life* Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2) Other Physical component between VNS and sham: *P* = 0.480, Mental Component between VNS and sham: *P* = 0.406

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• On/Off cycle parameters: 30 sec on and 5 min off • Duration of treatment: *Sham:* • Device implanted but not turned on		Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2) *MADRS* Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3) *IDS* Baseline n G1: 112 (115 randomized) G2: 110 Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5) *CGI-I* Baseline n G1: 112 G2: 110	*IDS* Endpoint score, mean (SD) NR % change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) *P* = 0.158 Responders, n G1: 19 (17) G2: 8 (7.3) *P* = 0.032 Remitters, n NR *CGI-I* Endpoint score, mean (SD) NR Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, *P* = 0.648	*Adverse Events* Overall, % NR Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:– • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%, • hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116)

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					12 events, involving 11 patients, were cases of worsening depression requiring hospitalization Cardiac SAEs during implantation: 1.7% v 0% COSTART used to code reported events *Attrition* Overall, % 1.3 (3/235) At end of treatment, % G1: 2.6 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 2.6 G2: 0 9 pts had a protocol violation post randomization *Adherence/ compliance* NR

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Stern et al., 2007[32] *Country, setting* NR, outpatient setting *Funding* The Milton Fund, NARSAD,Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Cienca *Research Objective* To test hypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in the analysis *N* 45 *Duration* • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse. Primary Outcome: HAM-D at 2 weeksnd and 2 weeks after treatment *Interventions* G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz toright DLPFC G4: Sham rTMS *Medications allowed* No psychotropic medications were allowed	*TRD definition* • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode *Tier 2* *Inclusion criteria* • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20 *Exclusion criteria* • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100 % MDD *Age, mean yrs* G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3 *Sex, % females* G1: 60 G2: 60 G3: 70 G4: 60 *Right handed, %* 100 *HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10 G4: 15 Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9)	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6) Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3) Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3) Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, *P* = 0.001	*Quality of Life* NR *Adverse Events* 9/45 pts reported severe headaches (pts by group NR); no seizures *Attrition* Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20 Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period.

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600	• H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy	G3: 27.9 (3.8) G4: 27.4 (2.9)	2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, P = 0.00001 Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0 At week 2 G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 (P < 0.0005) 1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 (P < 0.0005) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1/G3 vs. G2/G4 (P < 0.0005)	Reported in text as dropped out following week 2. *Adherence/ compliance* NR

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 Sham rTMS: • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above *Strategy* Switch Number of trains: 1 • Length of train			Remitters, n HAM-D ≤ 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%) G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 *P* = NS (all times); G2 vs. G4 and G1: vs. G3 *P* = NS (all times)	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Harley, 2008[36] *Country, setting* United States, university clinics, outpatient psychiatric *Funding* Kaplan Fellowship Award Grant through Harvard Medical School *Research Objective* To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 24 *Duration* Primary outcome after 16 weeks of active txt Follow-up: 6 months *Interventions* G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control *Medications Allowed* Patients continued antidepressant therapy *Strategy* Augmentation *Parameters* • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1	*TRD definition* • 1+ failed medications (6+ weeks at "standard effective dose") • Not required or not specified to be in current episode *Tier 2* *Inclusion criteria* • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study. *Exclusion criteria* • Borderline personaliy disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.	*Baseline N* G1: 13 G2: 11 *Treatment Failure* Mean failed trials NR *Polarity, %* MDD *Overall:* 100 *Age, mean yrs* Overall: 41.8 *Sex, % females* Overall: 75 *Race, % white* Overall: 83 *HAM-D 17* Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) *P* = NS *BDI* Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) *P* = NS	*HAM-D 17* Analyzed n G1: 10 G2: 9 Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23) Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78 *P* < 0.05 Remitters, n Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) *P* = NR *BDI* Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30) Change, mean (SD) G1: -12.80 G2: -1.55 *P* < 0.01	*Quality of Life* *Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT*) Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24) Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69) Change, mean (SD) G1: -1.3 G2: -0.33 *P* = NS *Social Adjustment Scale-Self-Report (SAS-SR) work subscale* Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions:16 G2: Wait list	• Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience			Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 *P* < 0.05 *Adverse Events* NR MMSE NR *Attrition* Overall, %: 21 At end of treatment, % G1:23 G2:18 At end of follow-up, % G1:20 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0 Withdrawals due to adverse events, % 0

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue in study and a medical problem prevented second from continuing. *Adherence/ compliance* Compliance Participants completed a weekly check-in form asking about medication compliance over preceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					forgotten a medication dose between 1 to 4 times in previous month.
Author, Year Paykel, 1999[38] Scott, 2000[59] Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219. *Country, setting* UK, outpatient *Funding* Medical Research Council, London, England and a grant from Oxford and Anglia Region *Research Objective* To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintenance treatment with antidepressants.	*Study design* RCT *Type of analysis* ITT *N* 158 *Duration* Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks. *Interventions* G1: Clinical management Only G2: CT plus Clinical Management *Medications allowed* Continued on current medications with dose adjustments allowed *Strategy* Augmention	*TRD definition* • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months. • Failure required to be in the current episode *Tier 2* *Inclusion criteria* • Unipolar depression, • aged 21 to 65 years,	*Treatment Failure* Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar 100% 100% *Age, mean yrs* G1: 43.2 (11.2) G2: 43.5 (9.8) *Sex, % females* G1: 53% G2: 46% *HAM-D 17* Baseline n G1: 78 G2: 80 Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7) *BDI* Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)	*HAM-D 17* G1: Clinical Management only G2: CT plus Clinical Management Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2) Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7) Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3) Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 *P* = NS Follow-up at 44 weeks G1: - 3.0 G2: -4.5 Follow-up at 68 weeks G1: -5.0 G2: -4.9	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 20% did not adhere to protocol through to study end or relapse point At end of treatment, % G1: 4 G2: 14 At end of follow-up, % G1: 12 G2: 10 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Quality Rating Good	*Parameters* Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16	• satisfying DSM-III-R17 criteria for major depression within last 18 months but not in last 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. *Exclusion criteria* • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm,		Responders, n NR Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45)) *BDI* Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6), Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3) Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7) Change, mean (SD) At week 20 G1: -6.24 G2: -8.44 Responders, n NR	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		• DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, •any other primary Axis I disorder at time of index illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions		Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%) Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36) Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93). Over 17 months relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				received CT. #2219: Relapse was defined as: (1) meeting DSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more on HAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms during follow-up phase between 2 successive ratings 2 months apart, reaching a score on HAM-D 17 of at least 13 on both occasions and a level of distress or dysfunction for which the withholding of additional active treatment was no longer justified	

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year McLoughlin et al., 2007[7] Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating major depressive	*Study design* RCT- pragmatic and single blinded (raters) *Type of analysis* m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months *Interventions* G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) *Polarity, %* MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % *Age, mean yrs* G1: 63.6 G2: 68.3 *Sex, % females* G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93 Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End ot treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
episodes in patients referred for ECT *Quality Rating* Good	*Strategy* Augmentation *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5		*BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25 Responders, n NR Remitters, n NR	suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR *Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					(verbal fluency, anterograde memory, and retrograde memory) *MMSE* Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year O'Connor, 2003[64] *Country, setting* United States, University Hospital, inpatient vs. outpatient population not clearly reported *Funding* NIH/NIMH and a NARSAD grant *Research Objective* Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition *Quality Rating* Poor	*Study design* Observational *Type of analysis* Completers *N* 28 *Duration* • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt *Medications allowed* rTMS patients completed a washout of all psychotropic medications while ECT continued all medications *Strategy* Switch strategy for rTMS and augment or add-on strategy for ECT group *Interventions* G1: ECT G2:	*TRD definition* • Patients referred for ECT • AD failures not required *Tier 3* *Inclusion criteria* • Met criteria for MDD • HRSD > 18 *Exclusion criteria* • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD *Age, mean yrs* G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2 *HAM-D* Baseline n Completers G1: 14 G2: 14 Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) *P* = 0.001 *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)	HAM-D Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5) Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time *P* < 0.01 Responders, n G1: NR G2: 0 Remitters, n G1: NR G2: 100% *Other* Validated measure Yes *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)	*Quality of Life* *Adverse Events* NR *Neuropsychological or executive functioning* Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning) Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09) Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00) Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: *P* > 0.05 G2: 44.07 (10.43)

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters ECT • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12, rTMS • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks			Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with2 week follow-up results ($P > 0.05$) No significant interaction between treatment sessions and groups with respect to LN ($P > 0.05$)	RAVLT, Acquisition, mean (SD) Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09). End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) $P < 0.01$. Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) $P > 0.05$. RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD) Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08) End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80) Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07). Transient News Events Test (TNET-measure of retrograde memory)

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12) Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33) Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12) Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$. Cognitive function/memory impairment reported as primary outcome measures. *MMSE* NR

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % No attrition At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year George et al., 1997[35] *Country, setting* USA, outpatient setting *Funding* NARSAD, Ted and Vada Stlanley Foundation *Research Objective* To test hypothesis: daily left prefrontal rTMS has antidepressant effects *Quality Rating* Fair	*Study design* RCT, crossover *Type of analysis* ITT *N* 12 *Duration* 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt *Interventions* G1: rTMS G2: sham stimulation *Medications Allowed* ADs tapered for 9, 3 partial responders continued their medication *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20	*TRD definition* • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV criteria for current MDD • right-handed *Exclusion criteria* • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma	*Treatment Failure* Number of previous AD medications Overall: 13.4 *Polarity, %* Unipolar Overall: 91.7 Bipolar II Overall: 8.3 *Age, mean yrs* Overall: 41.8 (12.4) *Sex, % females* Overall: 91.7 *Right handed, %* Overall: 100 *HAM-D 21* Baseline n G1: 12 G2: 12 Baseline score, mean (SD) Overall: 28.5 (4.2)	*HAM-D 21* G1: rTMS G2: sham stimulation Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 *P* < 0.03	*Quality of Life* NR *Adverse Events* Headache, % G1: 4/12 G2: NR Suicidality, % G1: 0 G2: Sham: 1/12 Seizures: None Unexpected side effects: None Headaches NR by active v. sham Memory or Attention: None *Attrition* Overall: 0 *Adherence/ compliance* N

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 2 • Inter-train interval: NR • Pulses per session: 800 • Total number of sessions: 5/wk for a total of 20 per patient Sham: • Same as above but angled at 45 degrees from skull				
Author, Year West, 198140 *Country, setting* UK, Hospital, inpatient *Funding* NR *Research Objective* The therapeutic effect of simulated and real bilateral electric convulsion therapy *Quality Rating* KQ1 - Fair	*Study design* RCT *Type of analysis* Completers or per protocol (PP) *N* 25 (22 analyzed) *Duration* 3 weeks *Interventions* G1: ECT G2: Simulated ECT *Medications Allowed* 50 mg amitryptyline *Strategy* Combination	*TRD definition* • Referred for ECT *Tier 3* *Inclusion criteria* • Primary depressive illness *Exclusion criteria* • NR	*Subgroups* NR *Baseline n* G1: 13 G2: 12 *Treatment Failure* NR *Polarity, %* NR *Patient Characteristics* *Age, mean yrs* G1: 52.0 G2: 53.3 *Sex, % females* G1: 45 G2: 36	*N Analyzed* G1: 11 G2: 11 *BDI* Yes G1: ECT G2: Simulated ECT Endpoint score, mean (SD) G1: 10.8 (SEM 2.6) G2: 22.2 (3.8) *P* < 0.002 Change, mean (SD) G1: -15.8 G2: -1.9 Responders, n NR	*Quality of Life* No *Adverse Events* NR *Neuropsychological or executive functioning* No Measures, Results None reported Predefined NA - No AE data reported Adequate information NA - No AE data reported

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters The anaesthetic agent was Althesin (alphadolone) and the muscle relaxant suxamethonium. Electric convulsion therapy was administered from a Transycon machine using 40 joules with double-sided unrectified waveform and bilateral anterior temporal placement of the electrodes.		*Race, % white* NR *Not Specified, %* NR Right handed, % NR *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) *BDI* Baseline score, mean (SD) G1: 26.6 (SEM 2.8) G2: 24.1 (3.5)	Remitters, n NR Other	*Attrition* Overall, % 12% At end of treatment, % G1: 15.4 G2: 8.3 At end of followup, % NR Withdrawals due to efficacy, % G1: 7.7 G2: 8.3 Withdrawals due to adverse events, % NR Other *Adherence/ compliance* None reported

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Rosa et al., 2006[2] *Country, setting* Brazil, university clinic, inpatients and outpatients included *Funding* Not reported *Research Objective* To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Included completers analysis & ITT (LOCF), ITT is reported in abstraction *N* 42 *Duration* Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk *Interventions* G1: ECT G2: rTMS *Medications allowed* ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed *Strategy* Switch	*TRD definition* • A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Age 18-65 • unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms *Exclusion criteria* • History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease • Use of cardiac pacemaker • Pregnancy	*Treatment Failure* Previous treatment, not specified, % Overall:100% *Polarity, %* Unipolar Overal: 100% *Age, mean yrs* G1: 46.0 G2: 41.8 *Sex, % females* G1: 46.7 G2: 60.0 *Race, % white* G1: 80.0 G2: 90.0 *HAM-D 17* Baseline n G1: 20 G2: 22 Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20] *CGI* Baseline n G1: 20 (N analyzed =15)	*HAM-D 17* Endpoint score, mean (SD) NR (graph only) Change, mean (SD) NR (graph only) *P* = 0.86 Responders, n (%) G1: 6 (20) G2: 10 (45) *P* = 0.35 Remitters, n (%) Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) *P* = 0.65 Instrument CGI Endpoint score, mean (SD) 2wk G1: 4.0 (1.0) G2: 3.7 (1.1) 4wk G1: 3.2 (1.5) G2: 3.1 (1.3) Change, mean (SD) NR, *P* = 0.672	*Quality of Life* NR *Adverse Events* Overall, % NR Suicidality, % G1: 10.0 G2: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study *Neuropsychological or executive functioning* NS differences between groups on all neuropsychological tests following wk2 & wk4. (Weschler Adult Intelligence Scale - R subtests (Vocabulary, Cube), Wechsler Memory Scale subtest (Digit Span), Rivermead Behavioral Memory Test) *MMSE* NR

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS: • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks *ECT:* • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5)		G2: 22 (N analyzed =20) Baseline score, mean (SD) G1: 4.7 (0.8) G2: 4.3 (0.8)		*Other* *Attrition* Overall, % 16.7 At end of treatment, % G1: 15.0* G2: 9.1* *Prior to completing txt (txt end date differed by pt) At end of follow-up, % G1: 25.0 G2: 9.1 Withdrawals due to efficacy, % G1: NR G2: 0.0 Withdrawals due to adverse events, % G1: NR G2: 9.1 Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy *Adherence/ compliance* NR

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Schulze-Rauschenbach et al., 2005[63] *Country, setting* Germany, Psychiatric University Hospital, inpatients *Funding* NR *Research Objective* To compare neurocognitive effects of unilateral ECT and rTMS using a control *Quality Rating* Fair	*Study design* Observational *Type of analysis* Observational study of patients completing txt *N* 30 *Duration* Not clear- testing took place 8.8 days on average afterlast treatment Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks. *Interventions* Control G1: ECT G2: rTMS *Medications Allowed* Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study	*TRD definition* • Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Consecutively admitted patients with DSM–IV diagnosis of MDD • Age over 18 years *Exclusion criteria* • Previous treatment with ECT or rTMS • Additional Axis I diagnosis	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 46.7 G2: 47.7 *Sex, % females* G1: 50 G2: 44 *HAM-D 17* Baseline n G1: 14 G2: 16 Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5) *BDI* Baseline n G1: 14 G2: 16 *SSMQ* Baseline n G1: 14 G2: 16	*HAM-D 17* Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9) Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, *P* = NS Responders, n G1: 6 (46%) G2: 7 (44%) *P* = 0.90 *BDI* Change, mean (SD) G1: 7.6 G2: 6.4Group x time, *P* = NS *SSMQ* Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8) Change, mean (SD) G1: 5.5 G2: 20.6	*Quality of Life* NR *Adverse Events* One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included. *Neuropsychological or executive functioning* Test scores ECT Pre / Post vs. rTMS Pre / Post Post; *P* = Post Ect vs. Post rTMS Learning and anterograde memory AVLT Immediate recall (trials 1-5); *P* = NS Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); *P* < 0.01 Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); *P* < 0.05 Recognition hits; *P* = NS and Recognition false alarms; *P* = NS MPT

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters ECT: • % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) rTMS • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: • Total number of sessions: 2-3/wk *Strategy* Augment or add-on		Baseline score, mean (SD) G1: -20.7 (19.0) G2: -16.8 (16.9)		Recall trial; *P* = NS and Delayed recall; *P* = NS Retrograde memory Retrograde AVLT Recall; *P* = NS and Recognition hits; *P* = NS Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); *P* < 0.05 Four-card task Free recall 2.0 (1.4) / 0.4 (0.5) vs. 1.4 / (1.2); *P* < 0.05 Recognition; *P* = NS AMI Recall score; *P* = NS Subjective memory SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); *P* < 0.05 Other cognitive functions MMSE; *P* = NS, TrailMakingTest A; *P* = NS, TrailMakingTest B; *P* = NS, Digit span (WAIS-R); *P* = NS, Letter-number span; *P* = NS, Word fluency (LPS); *P* = NS *MMSE* G1: ECT

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G2: rTMS G3: Control Baseline n G1: 14 G2: 16 G3: 15 Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0) Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1) Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01 Other *P* = NS *Attrition* Overall, % 3.3 At end of treatment, % G1: 7 G2: 0

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of follow-up, % G1: NR G2: NR Withdrawals due to efficacy, % G1: 0 G2: 0 Withdrawals due to adverse events, % G1: 7 G2: 0 One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included in analysis *Adherence/ compliance* NR

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Grunhaus et al., 2000[62] *Country, setting* Israel Sheba Medical Center, inpatients and outpatients *Funding* Established Investigator Award of NARSTAD *Research Objective* To compare rTMS to ECT and psychotic vs. non-psychotic *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 40 *Duration* Varied – ECT patients treated for average of 5 weeks, and rTMS pts treated for 4 weeks. Primary outcome measured at end of treatment *Interventions* Overall G1: ECT G2: rTMS Pts with psychosis G3: ECT: G4: rTMS Pts without psychosis G5: ECT G6: rTMS *Medications allowed* • ECT allowed benzodiazepines, neuroleptics antidepressants and	*TRD definition* • Pts referred for ECT: • Only some patients treatment resistant (not defined). Treatment failure not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • age over 18 • DSM-IV diagnosis of MDD • HAM-D17 ≥18 • no personal or first-degree relative history of seizure • no medical, neurological, or neurosurgical disorder that would preclude administration of ECT or rTMS. *Exclusion criteria* • Additional Axis-1 diagnoses	*Subgroups* Patients with and with out Psychosis *Treatment Failure* Failed ≤1 trial, % G1: 50 G2: 25 Failed ≥2 trials, % G1: 50 G2: 75 *Polarity, %* 100% MDD *Age, mean yrs* G1: 63.6 (15.0) G2: 58.4 (15.7) *Sex, % females* G1: 70 G2: 60 *HAM-D 17* Baseline n Overall G1: 20 G2: 20 Patients with Psychosis G3: 10 G4: 9 *Patients without* Psychosis G5: 10 G6: 11	*HAM-D 17* Endpoint score, mean (SD) At week 2 G1: 17.6 (7.4) G2: 19.3 (8.6) G3: 15.5 (7.6) G4: 23.4 (5.5) G5: 19.7 (7.0) G6: 15.8 (9.3) End of treatment G1: 11.2 (8.4) G2: 15.4 (7.5) G3: 8.4 (5.3) G4: 20.8 (5.0) G5: 13.9 (10.3) G6: 11.0 (6.2) Change, mean (SD) At week 2 G1: 10.8 G2: 6.5 G3: 16.0 G4: 5.3 G5: 5.5 G6: 7.7 End of treatment G1: 17.2 G2: 10.4 Group x time, *P* = 0.09 G3: 23.1 G4: 7.9 Group x time, *P* = 0.005 G5: 11.3	*Quality of Life* Scale Pittsburg Sleep Quality Index Intervention G1: ECT G2: rTMs G3: NR G4: ECT Psychotic vs none G5: rTMS Psychotic vs none Baseline n G1: 20 G2: 20 G3: NR G4: 10 vs. 10 G5: 9 vs. 11 Baseline score, mean (SD) G1: 12.5 (4.4) G2: 11.7 (5.7) G3: NR G4: 12.1 (5.5) vs 12.9 (3.1) G5: 14.1 (4.9) vs 9.7 (5.8) Endpoint score, mean (SD) G1: Awk2 8.8 (4.5) / endpoint 6.8 (3.5)

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	anticonvulsants in stable doses • rTMS All psychiatric medications were discontinued only clonazepam (1–2 mg/day, given in twice-daily doses) was started in all patients to decrease anxiety, provide relief of severe insomnia, and have an additional protective element regarding seizures *Strategy* Mixed-between group differences *Parameters* ECT: • % receiving bilateral: 40 switched after non-response • Intensity 2.5-fold seizure threshold • Number of sessions - mean 9.6 sessions (range 7-14) rTMS • Frequency (Hz):10 • Motor threshold (%):90 • Number of trains:NR		Baseline score, mean (SD) G1: 28.4 (9.3) G2: 25.8 (6.1) G3: 31.5 (11.5) G4: 28.7 (5.6) G5: 25.2 (5.3) G6: 23.5 (5.6)	G6: 12.5 Group x time, *P* = NS Responders if the final HRSD had decreased to 50% or more from baseline and the final GAS < 60. Responders, n End of txt G1: 16 (80%) G2: 9 (45%) G3: 10 (100%) G4: 2 (22%) *P* ≤ 0.01 G5: 6 (60%) G6: 7 (63%) *P* = NS	G2: Awk2 10.1 (3.7) / endpoint 10.5 (3.9) G3: NR G4: Awk2 8.0 (4.5) / endpoint 5.8 (2.1) vs G5: Awk2 12.2 (2.8) / endpoint 12.3 (3.6) vs. Awk2 8.4 (3.5) / endpoint 9.1 (3.8) Change, mean (SD) G1: Awk2 3.7 / endpoint 5.7 G2: Awk2 1.6 / endpoint 1.2 G3: G4: Awk2 4.1 / endpoint 6.3 vs Awk2 4.9 / endpoint 7.1 G5: Awk2 11.9 / endpoint 1.8 vs. Awk2 1.3 / endpoint 0.6 Other Overall Group F 1.8 (df 1,36) *P* = NS Time F 12.5 (df 2,72) *P* = 0.000 Interaction F 4.6 (df 2,2) *P* = 0.010 Non-psychotic Group F 0.5 (df 1,18) *P* = NS

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	•Length of train (seconds):2 or 6 • Inter-train interval:NR • Pulses per session: 400 or 1200 • Total number of sessions: 20				Time F 4.4 (df 2,36) *P* = 0.020 Interaction F 2.3 (df 2,2) *P* = NS Psychotic Group F 9.8 (df 1,16) *P* = 0.006 *Quality of Life* Overall Group F 1.8 (df 1,36) *P* = NS Time F 12.5 (df 2,72) *P* = 0.000 Interaction F 4.6 (df 2,2) *P* = 0.010 Non-psychotic Group F 0.5 (df 1,18) *P* = NS Time F 4.4 (df 2,36) *P* = 0.020 Interaction F 2.3 (df 2,2) *P* = NS Psychotic Group F 9.8 (df 1,16) *P* = 0.006 Scale Global Assessment of Function Scale Intervention G1: ECT G2: rTMS G3:

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G4: ECT Psychotic vs none G5: rTMS Psychotic vs none Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11 Baseline score, mean (SD) G1: 31.0 (8.5) G2: 34.1 (11.7) G3: Intervention4: 29.0 (7.0) vs. 33.0 (9.8) G5: 28.9 (9.9) vs. 38.3 (11.8) Endpoint score, mean (SD) G1: Awk2 46.8 (17.2)/ endpoint 61.5 (21.5) G2: Awk2 44.5 (14.7)/ endpoint 51.0 (18.2) G3: G4: Awk2 50.6 (18.3)/ endpoint 65.5 (18.8) vs. Awk2 43.0 (16.0)/ endpoint 57.5 (24.2) G5: Awk2 36.1 (8.2)/ endpoint 39.4 (14.5.) vs. Awk2 51.4 (15.5)/ endpoint 60.5

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Change, mean (SD) G1: Awk2 15.8 / endpoint 30.5 G2: Awk2 10.4 / endpoint 16.9 G3: G4: Awk2 21.6 / endpoint 36.5 vs. Awk2 10.0 / endpoint 24.5 G5: Awk2 7.2 / endpoint 10.5 vs. Awk2 13.1 / endpoint 22.2 Other Overall Group F 0.7 (df 1,38) *P* = NS Time F 40.8 (df 2,76) *P* = 0.000 Interaction F 3.4 (df 2,2) *P* = 0.040 Non-psychotic Group F 1.0 (df 1,19) *P* = NS Time F 19.8 (df 2,38) *P* = 0.000 Interaction F 0.3 (df 2,2) *P* = NS Psychotic Group F 8.2 (df 1,17) *P* = 0.01 *Adverse Events* NR 5 rTMS patients had mild headaches

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Neuropsychological or executive functioning Measures, Results MMS. (ECT baseline 25.9 (4.1), ECT end of treatment 24.5 (7.6); rTMS baseline 24.8 (4.1), rTMS end of treatment 26.3 (3.9), repeated measures ANOVA [group effect $F(1,29) = 0.1$, P = NS; time effect $F(2,58) = 1.3$, P = NS; interaction $F(2,2) = 2.3$, P = NS) analysis was also performed for psychotic–non-psychotic groups with similar results. Predefined No *MMSE* Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 25.9 (4.1) G2: 24.8 (4.1)

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Endpoint score, mean (SD) G1: 24.5 (7.6) G2: 26.3 (3.9) Change, mean (SD) G1: -1.4 G2: +1.5 Other ANOVA [group effect F(1,29) = 0.1, *P* = NS; time effect F(2,58) = 1.3, *P* = NS; interaction F(2,2) = 2.3, *P* = NS) analysis was also performed for psychotic–nonpsychotic groups with similar results. *Adequate information* *Attrition* Overall, % 0% At end of treatment, % 0 At end of follow-up, % 0 Withdrawals due to efficacy, % 0

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to adverse events, % 0 *Adherence/ compliance* Compliance All patients completed study

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Garcia-Toro et al., 2006[17] *Country, setting* Spain, single center, all outpatients *Funding* Fundacio La Marato de TV3 *Research Objective* To assess the efficacy of high and low frequency rTMS and different locations of activation *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 30 *Duration* • Primary outcome after 2 weeks of active treatment • Follow-up: 2 weeks post treatment *Interventions* G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam) *Medications allowed* All pts continued (failed) AD medication and other psychotropic meds *Strategy* Augmentation	*TRD definition* • Failed 2+ txt trials at 4+ weeks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • At least 18 yrs old, MDD, unipolar *Exclusion criteria* • Contraindications for rTMS and high suicide risk	*Subgroups* None *Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100% *Age, mean yrs* G1: 47.2 G2: 48.5 G3: 51.1 *Sex, % females* G1: 70 G2: 40 G3: 40 *Race, % white* NR *Right handed, %* G1: 90% G2: 100% G3: 100% *HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10) At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18) G3: 18.10 (6.15) Follow-up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0) Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%) At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), *P* = 0.048 Follow-up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%)	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in pharmacotherapy At end of treatment, % G1: 0 G2: 0 G3: 0 At end of follow-up, % NR Does not report which group 3 patients came from Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions ofbrain after examination with single photon emission

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS Low: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session: 1800 • Total number of sessions: 10 in 2 wks High • Frequency (Hz):20 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval: 20+5 • Pulses per session: 1200 • Total number of sessions: 10 in 2 wks Sham • Same but with coil angling 45 degrees away from scalp		Baseline score, mean (SD) G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14) *CGI-S* Baseline n G1: 10 G2: 10 G3: 10 Baseline score, mean (SD) G1: 4.7 (0.82) G2: 4.8 (1.0) G3: 4.8 (0.63)	G1: vs. G2+G3, *P* = 0.121 Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) *P* = NR *CGI-S* Endpoint score, mean (SD) At 2 weeks G1: 4.6 (0.97 G2: 3.8 (1.48) G3: 3.9 (0.99) 2 week follow-up G1: 4.75 (1.16) G2: 4.00 (1.15) G3: 3.7 (1.57)	computed tomography (20-Hz rTMS to an area of relatively low activity and 1- Hz rTMS to an area showing relatively high activate *Adherence/ compliance* Compliance all patients completed active 2 week treatment

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Avery et al., 2006[10] *Country, setting* USA, Single center, University department of psychiatry, outpatient *Funding* NIMH *Research Objective* To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation *Quality Rating* Good Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)	*Study design* RCT *Type of analysis* ITT *N* 68 *Duration* 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint *Interventions* G1: High-left TMS G2: Sham *Medications Allowed* • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)	*TRD definition* • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode *Tier 1* *Inclusion criteria* • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day *Exclusion criteria* • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence with inpast 2 years, • antisocial or borderline personality disorder,	*Subgroups* Pain, subgroup analysis presented in Avery et al, 200711 Baseline n G1: 35 G2: 33 *Treatment Failure* Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72) *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 44.3 G2: 44.2 *Sex, % females* G1: 60 G2: 52 *Race, % white* NR *Right handed, %* NR	*HAM-D 17* Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time *P* = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) *P* = 0.008 Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) *P* = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) *BDI* Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed significant group by time interaction (*P* = 0.003)	*Quality of Life* NR *Adverse Events* Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, *P* < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks Sham • Identical stimulation parameters • Lateral edgeof coil rotated 90° away from scalp	• active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity	Groups similar at baseline Yes *HAM-D 17* Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9) *BDI* Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)		*Neuropsychological or executive functioning* No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS[11]: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$) no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures.models were refit withoutinteraction term, there was no significant treatment group main effect ($P > 0.05$) evident for any ofneuropsychological tests, indicatinggroups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					improvement in individual neuropsychological test performances for both groups. No confusion was associated with TMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session. *MMSE* NR *Attrition* Overall, % 7.4% (5/68) At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 3.0 Withdrawals due to adverse events, % G1: 0 G2: NR

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Very unclear as to when patients discontinued *Adherence/ compliance* NR
Author, Year Bretlau, 2008[41] *Country, setting* Denmark, setting NR, outpatients *Funding* Commercial source-please list name.supported by Medicon Valley Academy and an unrestricted research grant from H Lundbeck A/S *Research Objective* To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment *Quality Rating* Fair	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 49 *Duration* 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. Escitalopram was administered during the entire trial at 20mg daily (10 mg daily for first wk of trial). Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals.	*TRD definition Required to be in current episode* Yes *Setting(s)* Not clearly reported *Inclusion criteria* Aged 18 - 75 years; meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); failed to respond to at least one previous adequate (at least 6 weeks) antidepressant treatment during the current episode; subjects with heart disorders or diabetes were included if they were in a somatically stable phase	*Subgroups* No sub-group analysis Treatment Failure Failed 1 or more, % G1: 100 G2: 100 Failed 2 or more, % G1: NR G2: NR Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9) Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR	*HAM-D* Yes HAM-D 17 Other, please describe.HAM-D 6 G1: rTMS + escitalopram G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5) Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1), Awk3 = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU	*Quality of Life* NR Adverse Events Overall NR Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00 Cardiovascular adverse events, % G1: palpatations: 3wk/ 12 wk mean: 0.23/0.14 G2: 0.30/0.12 Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22 Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Interventions B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n= 24) G1: rTMS + escitalopram G2: sham TMS + escitalopram G1: rTMS + escitalopram** G2: sham TMS + escitalopram** *Parameters* Location = Left Dorslateral prefrontal cortex Frequency = 8 Hz Intensity = 90% motor threshold Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. Number of sessions = 15	*Exclusion criteria* Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders; potentail risk factors for escitalopram such as hypersensitivity to the Intervention, intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, pregnancy or insufficient contraception in females of reproductive age; risk factors for TMS such as history of epilepsy, metal implants in the head or neck regions, pacemaker or other electronic implants, receiving antipsychotics; having major suicide ideation.	Bipolar II G1: NR G2: NR *Patient Characteristics* *Age, mean yrs* G1: 53.1 G2: 57.8 *Sex, % females* G1: 68% G2: 57% *Race, % white* G1: NR G2: NR *Not Specified, %* G1: NR G2: NR *Right handed, %* G1: NR G2: NR Groups similar at baseline Yes *Tier* Tier 22A: 1+ failed, MDD	wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2) Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2 Responders, n G1: NR G2: NR Remitters, n G1: NR G2: NR	Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39 Somnolence, % NR Suicidality, % NR Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (P <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse events inlcude: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63);

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Strategy Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment			*Other* The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favour of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.83 (0.22-1.44), P = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.78 (0.18 - 1.39), P = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.48(-0.12 - 1.07), P = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.64 (0.04 - 1.24),	Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12=0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36);

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				P = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.47 (-0.11 - 1.07), P = 0.22; HAM-D6 Awk 2 Effect size (95% CI) and Mann-Whitney P: 0.73 (.018 -1.39), P = 0.05; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.80 (0.20 - 1.42), P = 0.01; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.09 -1.29), P = 0.02; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney P:0.50 (-0.10 - 1.09), P = 0.10; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.0.50 (-0.10 - 1.09), P = 0.09;	Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); Neuropsychological or executive functioning No Measures, Results NR Predefined Yes MMSE No NR Baseline n NR Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) NR

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				BDI G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0) Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7), FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9) Change, mean (SD) G1: 12.4 G2: 9.4	Other Yes Study utilized the UKU scale as listed before - Other adverse events inlcude: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Responders, n NR Remitters, n NR Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.73 (0.12 - 1.33), P = 0.03; Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.84 (0.24 -1.46), P = 0.00; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.64(0.02 -1.22), P = 0.03; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.04 - 1.24), P = 0.03; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.46 (-0.12 - 1.06), P = 0.12;	12 =0.94 (0.73); rTMS A wk = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00); Adequate information Yes Attrition Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out.

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				MADRS NR *IDS* NR *CGI-S* NR *CGI-I* NR Instrument Major Depression Inventory (MDI) Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6) Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7)	At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0 At end of follow-up, % G1: 21% G2: 4% Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Adherence/ compliance NR

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8) Change, mean (SD) G1: 17.4 G2: 14.4 MDI Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.36 (-0.23 - 0.94), P = 0.18; Awk 3 Effect size (95% CI) and Mann-Whitney P:0.43 (-0.16 - 1.03), P = 0.29; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.29 (-0.29 - 0.88), P =0.20; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.22 (-0.36 - 0.81), P = 0.72; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.23 (-0.36 -0.81), P = 0.43;	

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Holtzheimer et al., 2004[19] *Country, setting* USA, single center, outpatient/inpatient status not clearly stated *Funding* University of Washington *Research Objective* Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 15 *Duration* Primary endpoint following 2 weeks of treatment and follow-up 1 week after txt completed *Interventions* G1: rTMS G2: Sham *Medications Allowed* All pts discontinued (failed) AD medication *Strategy* Switch *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5 • Inter-train interval: 30-60	*TRD definition* • Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18 *Exclusion criteria* • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy	*Treatment Failure* Failed 7 or more, % G1: 85.7 G2: 37.5 *Polarity, %* Unipolar 100% MDD *Age, mean yrs* G1: 40.4 G2: 45.4 *Sex, % females* G1: 57.1 G2: 42.9 *Right handed, %* G1: 100 G2: 100 *HAM-D 17* Baseline n G1: 7 G2: 8 Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3) *BDI* Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)	*HAM-D 17* Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7) At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0) 1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8 At week 2 G1: 8.1 G2: 5.5 1 week follow-up G1: 3.9 G2: 3.2 All endpoints, *P* = NS Responders, n (%) At week 1 G1: 0 G2: 0 At week 2 G1: 2 (28.6) G2: 1 (12.5)	*Quality of Life* NR *Adverse Events* No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated. *Neuropsychological or executive functioning* Both groups performed equally well with exception of one measure of verbal memory, Trial 7 ofRey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); *P* < 0.05). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Pulses per session: 1600 • Total number of sessions: 10 over 2 wks Sham rTMS • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp			1 week follow-up G1: 0 G2: 0 *BDI* Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7) At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4) 1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9) Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1 Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), *P* = NS	*MMSE* NR There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated. *Attrition* Overall, % 0 during treatment. 3 (20%) before final assessment at week 3 At end of treatment, % 0 At end of follow-up, % G1: 28.6 G2: 12.5 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Other NR

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adherence/ compliance Compliance All 15 subjects completed all 10 txt sessions

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Boutros et al., 2002[13] *Country, setting* US, Yale School of Medicine and VA-Connecticut, outpatient *Funding* VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer *Research Objective* To provide additional data on effiacy and safety for rTMS as an augment strategy in TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 21 *Duration* 2 weeks txt; follow-up with responders for up to 20 weeks post txt *Interventions* G1: rTMS G2: Sham *Medications Allowed* Pts allowed to continue all current psychotropic meds *Strategy* Augmentation, 3 pts in active and 1 in sham txt were not on any meds *Parameters* rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major Depression • HAM-D25 >= 20 *Exclusion criteria* • Suicidality • "Prominent" psychotic sympotms • History of neurological disorders • current drug abuse	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar Overall: 100% *Age, mean yrs* G1: 49.5 G2: 52.0 *Sex, % females* G1: 25 G2: 10 *Right handed, %* G1: 90.9 G2: 88.9 HAM-D Baseline n G1: 12 G2: 9 Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)	*HAM-D* Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 *P* = NS Responders, n Defined as 30% improvement on HAM-D G1: 7 G2: 2 Responders, n (%) Defined as 50% improvement on HAM-D G1: 3 G2: 2 *Relapse* Of 6 active treatment responders inluded in20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in thh 20-week follow-up, 1 relapsed.	*Quality of Life* NR *Adverse Events* Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6 Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR *Attrition* Overall, % 18.2% (4/22) At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10) At end of follow-up, % NR

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: 58 • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp				Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR *Adherence/ compliance* NR
Author, Year Fitzgerald et al., 2006[14] *Country, setting* Australia, single center *Funding* Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald) *Research Objective* rTMS versus placebo for depression	*Study design* RCT *Type of analysis* ITT (LOCF) *N* 50 *Duration* 2 wks double blind with those with >20% decrease in MADRS to continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary outcome after 2 and 6 weeks of txt	*TRD definition* • 2+ failed medications with txt duration ≥6 wks • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • DSM-IV diagnosis of Major Depressive Episode • MADRS ≥ 20 *Exclusion criteria* • Significant medical illness • Neurological disorders • Other axis I psychiatric disorders	*Treatment Failure* Mean failed AD trials (lifetime) G1: 5.6 (3.1) G2: 6.2 (3.0) *Polarity, %* Unipolar G1: 84% G2: 84% Bipolar G1: 16% G2: 16% *Age, mean yrs* G1: 46.8 G2: 43.7 *Sex, % females* G1: 60 G2: 64	HAM-D 17 Endpoint score, mean (SD) NR Change, % decrease (SD) G1: 45.2% (40.1) G2: 5.4% (23.1) *P* < 0.001 Change, mean G1: -10.17 G2: -1.07 Responders, n (%) At 6wks G1: 13 (52.0) G2: 2 (8.0) *P* = 0.001	*Quality of Life* GAF Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9) Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [*P* <0.05] Change, mean (SD) G1: 10.2 G2: 1.1 GAF Scale (t=2.0, df=40.2, *P* < 0.05)

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Quality Rating Good	*Interventions* G1: rTMS G2: Sham *Medications allowed* • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, • Antipsychotic medication, • Benzodiazepines *Strategy* Augmentation, 23% not taking medication at study entry *Parameters* rTMS Low Right: Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 3 • Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 Sequential High Left: • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15		HAM-D 17 Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4) BDI Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9) MADRS Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)	Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0) *P* = NR BDI Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7) At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8) At 6 weeks G1: 9.2 (6.7) G2: NR Change, mean (SD) At week 2 G1: 10.9 G2: 7.7 At 4 weeks G1: 18.7 G2: 8.3 At 6 weeks G1: 20.0 G2: NR, *P* = 0.01 Responders, n NR	*Adverse Events* Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved ondigit span backward test improved in rTMS only (group by time: *P* = 0.07). Controlled Oral Word Association test improved for both groups (time: *P* = 0.001). Nausea 12% vs. 0, No seizures or manic episodes; *Neuropsychological or executive functioning* Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction Digit span backward Test Performance improved in rTMS only (group by time: *P* = 0.07).

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 • Total number of sessions: 10 sessions/day, 5 days/wk Sham: • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides)			Remitters, n NR MADRS Endpoint score, mean (SD) At week 2 G1: 26.2 (10.2) G2: 30.9 (8.2) At week 4 G1: 11.7 (7.1 G2: 34.5 (12.0) At week 6 G1: 8.9 (7.9) G2: NA Change, mean (SD) At week 2 G1: 7.8 G2: 3.2 At week 4 G1: 22.3 G2: 0.4 (increased) At week 6 G1: 25.1 G2: NA Group by time, *P* = 0.001 at all time points Responders, n At 6 weeks G1: 11	Controlled Oral Word Association Test Improved for both groups *P* = 0.001 MMSE NR *Other* Nausea 12% vs. 0 No seizures or manic episodes; *Attrition* Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78 After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn At end of treatment, % G1: 0 G2: 12 At end of follow-up, % G1: 56 G2: 100

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: 2 *P* < 0.05 Remitters, n MADRS < 10 At 6 weeks G1: 9 G2: 0 *P* = 0.005 At week 2 G1: 2 G2: 0 Follow-up at week 3 G1: 3 G2: 0 Follow-up at week 4	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR
Author, Year Fitzgerald et al., 2003[15] *Country, setting* Australia 2 general psychiatric services, outpatients *Funding* National Health and Medical Research Council and a grant fromStanley Medical Research Institute	*Study design* RCT *Type of analysis* ITT *N* 60 Tier 1 *Duration* Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up	*TRD definition* • Failed a minimum of 2 courses of antidepressant medications (6+ weeks) Not required or not specified to be in current episode *Inclusion criteria* • DSM-IV diagnosis of Major Depression (included bipolar depression)	*Treatment Failure* Mean failed trials Overall (SD) 5.68 (3.40) Polarity, % Bipolar I G1: 5 G2: 5 G3: 20 *Age, mean yrs* G1: 42.2 G2: 45.55 G3: 49.15	BDI Endpoint score, mean (SD) At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7) Change, mean (SD) At 2 weeks G1:- 6.4 G2: -7.8 G3: -2.3 *P* = 0.03	*Quality of Life* GAF Global Assessment of Functioning Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Research Objective To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group *Quality Rating* Good	assessment conducted at 2 weeks post txt. *Interventions* G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham *Medications Allowed* 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics *Strategy* Augmentation *Parameters* rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week	*Exclusion criteria* • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders	*Sex, % females* G1: 40 G2: 35 G3: 55 *Right handed, %* G1: 90 G2: 100 G3: 85 BDI Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10) MADRS Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)	MADRS Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5) Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) *P* = 0.004 G1: vs. G3, G2 vs. G3, *P* < 0.005 Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) *P* = 0.07 Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 *P* = NR	Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8) Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Quality of Life* Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Adverse Events* Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week			CGI Endpoint score, mean (SD) NR *P* =.01	(10%) reported a headache after rTMS. Although there was no difference in incidence of these adverse effects (*P* =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour. Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Neuropsychological or executive functioning • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance onverbal paired associates (t50=−7.3; *P* < 0.001), verbal fluency (t48=−3.8; *P* < 0.001), and digit span forwards (t48=−1.8; *P* = 0.003) subscales;Personal Semantic Memory Schedule (t50=−2.4; *P* = 0.02); andAutobiographical Memory Schedule (t50=−1.9; *P* = 0.05). • A similar pattern of improvements was seen for each oftreatment subgroups (HFL-TMS

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					only, LFR-TMS only, or both active treatments). • Changes in performance oncognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores acrosssame times. MMSE NR *Other* *Attrition* Overall, % None in initial 2 week treatment phase At end of treatment, % 0 At end of follow-up, % NR But at least 28.3% did not continue on thru2nd 2 weeks Withdrawals due to efficacy, % NR Withdrawals due to adverse events, %

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear *Adherence/ compliance* NR

Evidence Table 33. KQ 4. Adherence: Tier 1 (ECT vs. pharma—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Folkerts et al., 1997[42] *Country, setting* Germany, single center, inpatients *Funding* Not reported *Research Objective* To compare ECT in a controlled, randomized study withserotonin reuptake inhibitor paroxetine in treatment-resistant depression. *Quality Rating* Fair	*Study design* RCT *Type of analysis* per protocol *N* 39 *Duration* Total 6 weeks; Wash-out >= 3days; Phase I ECT - 2wks, Paroxetine - 4 wks; Phase II Paroxetine group - if clinical improvement reduction < 50% treatment switched to ECT, ECT group crossed over to Paroxetine or other antidepressants. *Interventions* G1: ECT G2: Paroxetine *Medications Allowed* After med wash -out patients were allowed a tranquillizer (diazepam up to 5 mg daily), a sedative (lormetazepam 0.5- 1.0 mg or triazolam 0.25 mg) or a sedative neuroleptic	*TRD definition* • 2+ failed treatmentd (8+ weeks) including at least 1 tricyclic, at a dosage of at least 100 imiprimine equivalents • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Major depressive episode single and recurrent • Bipolar disorders • HAM-D21 >=22 *Exclusion criteria* • Psychosis • Pronounced suicidal tendency • Severe physical illness • History of substance abuse • previous paroxetine or ECT treatment	*Treatment Failure* Level of tx resistance (Kuhs, 1995) G1: 1.9 (0.7 SD) G2: 2.0 (0.8 SD) Mean failed trials G1: 4.9 G2: 4.3 *Polarity, %* Unipolar G1: 90.5 G2: 83.3 Bipolar G1: 9.5 G2: 16.7 *Age, mean yrs* G1: 47.6 G2: 52.3 *Sex, % females* G1: 62 G2: 44 HAM-D 21 Baseline n G1: 21 G2: 18 Baseline score, mean (SD) G1: 31.1 (4.9) G2: 32.6 (5.4)	HAM-D 21 Endpoint score, mean (SD) Endof Phase I (ECT: 2-3 wks, Paroxetine: 4 wks) G1: 12.5 (3.9) G2: 23.0 (10.4) Endof Phase II (open trial, 6 weeks) G1: 12.8 (5.1) G2: 15.2 (7.9) Change, mean (SD) End of Phase I G1: -18.6 G2: -9.6 % Reduction in HAM-D, *P* = 0.001 End of Phase II G1: 18.3 G2: 17.4 Responders, n End of Phase I G1: 15 (71.4%) G2: 5 (27.8%) *P*= 0.006	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 0 - all patients continued toscheduled end of treatment At end of treatment, % 0 At end of follow-up, % 0 Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* • All pts continued their respective therapsies through scheduled end of treatment Phase I • 11 of 21 ECT were able to discontinue after 6th ECT session and 10 pts. had 3

Evidence Table 33. KQ 4. Adherence: Tier 1 (ECT vs. pharma—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	(pipamperon, up to 40 mg daily). *Parameters* ECT: • % receiving bilateral: 0 • Intensity: 2.5-fold seizure threshold • Number of sessions (range, mean, SD): 3/wk, range 6 to 9, mean 7.2 session Paroxetine • Started at 20 mg/day, within 7 days increased to 40 mg, allowed up to 50 mg, mean dose 44 mg/day for at least 4 weeks *Strategy* Switch				additional ECT treatments. • Phase II - of ECT group, 9 received paroxetine and 12 received other antidepressants • Of paroxetine groups, 7 crossed over to ECT • 11 received antidepressants - 7 paroxetine and 4 received other antidepressants 1 person was excluded from analysis due to failure to increase treatment dosage

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Stern et al., 2007[32] *Country, setting* NR, outpatient setting *Funding* The Milton Fund, NARSAD,Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Cienca *Research Objective* To testhypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in the analysis *N* 45 *Duration* • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse. Primary Outcome: HAM-D at 2 weeksnd and 2 weeks after treatment *Interventions* G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz toright DLPFC G4: Sham rTMS *Medications allowed* No psychotropic medications were allowed	*TRD definition* • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode *Tier 2* *Inclusion criteria* • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20 *Exclusion criteria* • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar 100 % MDD *Age, mean yrs* G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3 *Sex, % females* G1: 60 G2: 60 G3: 70 G4: 60 *Right handed, %* 100 *HAM-D 21* Baseline n G1: 10 G2: 10 G3: 10 G4: 15 Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)	*HAM-D 21* Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6) Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3) Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3) Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, *P* = 0.001	*Quality of Life* NR *Adverse Events* 9/45 pts reported severe headaches (pts by group NR); no seizures *Attrition* Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20 Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period.

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1	• Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy		2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, $P = 0.00001$ Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0 At week 2 G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$) 1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0	Reported in text as dropped out following week 2. *Adherence/ compliance* NR

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Sham rTMS: • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above *Strategy* Switch			G1/G3 vs. G2/G4 ($P < 0.0005$) Remitters, n HAM-D ≤ 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%) G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 P = NS (all times); G2 vs. G4 and G1: vs. G3 P = NS (all times)	

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year O'Reardon, 2007[31] *Country, setting* US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported *Funding* Neuronetics *Research Objective* To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral perfrontal cortex is effective and safe inacute treatment of major depression *Quality Rating* Good	*Study design* RCT *Type of analysis* Modified ITT (m-itt) *N* 325 randomized *Duration* 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over aftr 4 weeks if not responding. *Interventions* G1: Active TMS G2: Sham TMS *Medications Allowed* All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use of hypnotics, anxiolytics for txt emergent insomnia or anxiety *Strategy* Switch	*TRD definition* • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime *Tier 2 Setting(s)* Not clearly reported *Inclusion criteria* • Aged 18—70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed atscreening assessment *Exclusion criteria* • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder	*Baseline N* G1: 165 G2: 160 Current episode failures, meanG1: 1.6 G2: 1.6 Mean failed trials NR Previous treatment, not specified, % NR *Polarity, %* Unipolar 100 *Age, mean yrs* G1: 47.9 G2: 48.7 *Sex, % females* G1: 55.5% G2: 50.7% *Race, % white* G1: 94.2% G2: 89.7% HAM-D 17 Baseline score, mean (SD) G1: 22.6 (3.3) G2: 22.9 (3.5)	*HAM-D 17* Analyzed n G1: 155 G2: 146 Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5 At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0) Change, mean (SD) At week 2 G1: -5.2 G2: -3.5 At week 6 G1: -5.5 G2: -3.3 *P* = 0.005 Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9) *P* > 0.10 At week 4 G1: 32 (20.6) G2: 17 (11.5) *P* < 0.05	*Quality of Life* NR *Adverse Events* Serious adverse events G1: 6 G2: 5 Suicidality, % G1: 0.6 G 2: 1.9 • Exacerbation of depression: active TMS = 0.6%, sham TMS = 1.9% • Eye pain: active TMS = 6.1% sham TMS = 1.9%; • GI disorders toothache: active TMS = 7.3%, sham TMS = 0.6%; • Application site discomfort: TMS = 10.9%, sham = 1.3% • Application site pain, %: TMS = 35.8, sham = 3.8 • Facial pain: active TMS = 6.7%, sham TMS = 3.2 • Muscle twitching: TMS = 20.6%, sham = 3.2% • Pain of skin: TMS = 8.5%, TMS = 0.6%

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters rTMS • Frequency (Hz): 10 • Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks rTMS Sham: • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil	• Posttraumatic stress disorder and eating disorders (if present in past year) • Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head	MADRS Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 32.8 (6.0) G2: 33.9 (5.7) IDS Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 42.0 (9.4) G2: 43.4 (9.9) CGI-S Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 4.7 (.6) G2: 4.7 (.7)	At week 6 G1: 38 (24.5) G2: 20 (13.7) *P* < 0.05 Remission rate n (%) HAM-D17 < 8 At week 2 G1: 5 (3.2) G2: 3 (2.1) *P* > 0.10 At week 4 G1: 110 (7.1) G2: 9 (6.2) *P* > 0.10 At week 6 G1: 24 (15.5) G2: 13 (8.9) *P* = 0.065 MADRS Endpoint score, mean (SD) At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1) At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8) Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1	MMSE NR *Attrition* Overall, % 15 At end of treatment, % G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6% At end of follow-up, % G1: NR G2: NR Withdrawals due to efficacy, % G1: 0.6% G2: 1% Withdrawals due to adverse events, % G1: 5% G2: 4% Other • 325 subjects were randomized • 24 were "nonevaluable" • 301 continued to receive at least 1 treatment, these 301 were included in final analysis • 277 completed study through week 4.

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				At 6 weeks G1: 6 G2: 3.9 *Response rate, %* At week 2 G1: 8.4 G2: 6.2 *P* > 0.10 At week 4 G1: 18.1 G2: 11.0 *P* <0.05 At week 6 G1: 23.9 G2: 12.3 *P* <0.01 Remission rate, % Remission defined as total score <10 At week 2 G1: 3.9 G2: 2.1 *P* > 0.10 At week 4 G1: 7.1 G2: 6.2 *P* > 0.10 At week 6 G1: 14.2 G2: 5.5 *P* < 0.05	*Adherence/ compliance* NR

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Berman et al., 2000[28] *Country, setting* US, urban community health center, inpatient and outpatients *Funding* Veterans Administration, NIMH, State of CT Research Objective To assessefficacy of rTMS in unmedicated TRD patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 20 *Duration* 2 weeks (10 weekdays of txt) Primary outcome = HAM-D at 2wks *Interventions* G1: rTMS G2: Sham TMS *Medications Allowed* All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep *Strategy* Switch *Parameters* rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imiprimine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode *Tier 2* *Inclusion criteria* • Current Major depressive episode (via Ham-D) *Exclusion criteria* • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control	*Treatment Failure* Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup) *Polarity, %* Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 *Age, mean yrs* G1: 45.2 G2: 39.4 *Sex, % females* G1: 20 G2: 40 *Race, % white* G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic) *HAM-D 25* Baseline n G1: 10 G2: 10	*HAM-D 25* G1: rTMS G2: Sham TMS Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) *P* < 0.05 Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 *P* = 0.09 Three partial responders symptom severity returned to baseline within 1-2 weeks *BDI* Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) *P* = 0.27	*Quality of Life* NR *Adverse Events* Headache, n G1: 60 G2: 50 Difficulty starting urination great in active group *P* = 0.03 Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) • Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appétit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days Sham • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp		Baseline score, mean (SD) G1: 37.1 G2: 37.3		coordination, and muscle stiffness MMSE NR *Attrition* Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0 *Adherence/ compliance* NR

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year George, 2010[18] George *Country, setting* United States, outpatient *Funding* NIMH as the Optimization of TMS for the Treatment of Depression Study *Research Objective* To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder *Quality Rating* Good	*Study design* RCT *Type of analysis* mITT (all randomized patient who started at least 1 treatment session) Completer (randomized patients who were treated according ot protocol and had fewer than 4 rescheduled, missed, or partially completed rTMS sessions dueing weeks 2 to 6) Fully Adherent (fewer than 2 rescheduled, missed, or partially complete sessions; must not have been taking prohibited psychiatric medications or illicit drugs; and had no other protocol violations) *N* Randomized: 199 ITT: 190 Completers: 154 Adherent: 120 *Duration* Fixed Duration Active Treatment: 3 wks Variable Duration Active	*TRD definition* • Moderate level of treatment resistance as defined by the ATHF; insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥ 3 trials; Author personal communication states, "All patients had either one failed antidepressant failure, or multiple intolerance to antidepressant medications." • Not required in the current episode *Tier 2* *Inclusion criteria* • Antidepressant medication-free outpatients; 18-70 yo; DSM-IV MDD, single or recurrent; HAM-D24 ≥ 20; Stable during 2wk medication-free lead-in; moderate level of treatment resistance as defined by the Antidepressant Treatment History Form (ATHF); insufficient clinical benefit to 1-4 adequate	*Subgroups* No Subgroups *Baseline n* mITT G1: 92 G2: 98 *Treatment Failure* Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR Current episode failures, mean Mean, median (SD) G1: 1.62, 1 (1.37) G2: 1.41, 1 (0.97) Mean failed trials Mean, median (SD) G1: 3.34, 2 (2.68) G2: 3.28, 3 (2.11) *Polarity, %* Unipolar G1: 100 G2: 100 Bipolar I G1: 0 G2: 0	*HAM-D (Insert #)* Yes HAMD24 G1:rTMS G2: Sham N Analyzed mITT G1: 92 G2: 98 Observed: G1: 92 G2: 98 Observed Endpoint: G1: 83 G2: 91 Completers: G1: 72 G2: 82 Fully Adherent: G1: 57 G2: 63 Endpoint score, mean (SD) Observed G1: 21.61 (9.26) G2: 23.38 (7.43) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -4.23 to 0.10, -0.42, p = 0.06 Change, mean (SD) Observed at 3 weeks G1: -4.65 (NR) G2: -3.13 (NR)	*Quality of Life* No *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % NR Dizziness, % NR Headache, % G1: 32 G2: 23 Insomnia, % G1: 7.6 G2: 10 Post op complications, % NR Somnolence, % G1: 5 G2: 4 Suicidality, % Suicidality: NR

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Treatment: 3 wks No-treatment lead-in: 2 wks HAM-D assessment performed twice weekly Acute trial terminated when patients met the stable remission criteria. *Interventions* rTMS Sham G1: rTMS G2: Sham G1: rTMS G2: Sham G1:rTMS G2: Sham *Medications Allowed* None (2 week washout) *Strategy* Switch strategy *Parameters* G1: Location: Left prefrontal cortex Frequency: 10 Hz Intensity 120% MT Pulses: 10 pulses per second for 4 seconds; 3000 persession Intertrain interval: 26 seconds Length of Session: 37.5 minutes (75 trains)	medication trials or intolderant to ≥ 3 trials. *Exclusion criteria* • Other current Axis I disorders; past failure to respond to an adequate trial of ECT; prior treatment with TMS or VNS; personal or close family history or seizure disorder; Neurologic disorder; Ferromagnetic material in body or close to head; pregnancy; taking meds known to lower seizure threshold.	Bipolar II G1: 0 G2: 0 *Patient Characteristics* *Age, mean yrs* G1: 47.7 G2: 46.5 *Sex, % females* G1: 63 G2: 51 *Race, % white* G1: NR G2: NR *Not Specified, %* G1: NR G2: NR *Right handed, %* G1: NR G2: NR Groups similar at baseline Yes HAM-D 17 Baseline score, mean (SD) G1: 26.3 (5.0) G2: 26.5 (4.8) BDI *Baseline score, mean (SD)*	Responders, n mITT: G1: 14 G2: 5 p = 0.009 OR of responding to rTMS vs. Sham 4.6 (95%CI, 1.47 to 14.42) Completer: G1: 10 G2: 4 p = 0.02 Fully Adherent: Overall = 7 p = 0.14 Remitters, n No. (95%CI) mITT: G1: 13 (8.5 to 22.7) G2: 5 (2.3 to 11.4) OR (95%CI): 4.18 (1.32 to 13.24) Completers: G1: 10 (7.8 to 23.7) G2: 4 (2.0 to 11.9) OR (95%CI): 4.92 (1.29 to 18.76) Fully Adherent: G1: 6 (5.0 to 21.2) G2: 2 (1.0 to 10.8) OR (95%CI): NS Remitters by Treatment Phase Phase I Fixed(Wks 1-3) G1: 6 G2: 2 Phase I Variable (Wks 4-6)	Suicides: G1: 0 G2: 0 Additional Comments Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Fixed Active Treatment - Number of sessions: daily weekday sessions (15 sessions) Blinded treatment for improvers - Number of sessions: daily weekday sessions for up to another three weeks (total possible sessions = 30) G2: Similar coil as active treatment witha metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.			Week 4 Day 2 G1: 2 G2: 0 Week 4 Day 5 G1: 3 G2: 0 Week 5 Day 2 G1: 2 G2: 3 Other Response: ≥ 50% decrease in HAM-D score from baseline) Remission: HAM-D score of 3 or less or 2 consecutive Ham-D scores less than 10 MADRS Yes G1: rTMS G2: Sham Baseline n Observed Baseline G1: 92 G2: 98 Observed End of Phase I G1: 83 G2: 91 Baseline score, mean (SD) G1: 29.5 (6.9) G2: 29.8 (6.4)	Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient *Neuropsychological or executive functioning* No Measures, Results NA Predefined No MMSE No Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other *Other* Yes Those not reported previously below: Discomfort at the

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Endpoint score, mean (SD) Observed at 3 weeks G1: 24.59 (11.44) G2: 27.75 (9.06) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -6.10 to -0.76, -0.51, p = 0.01 Change, mean (SD) Observed at 3 weeks G1: -4.89 (NR) G2: -2.06 (NR) Responders, n NR Remitters, n NR Other NA IDS Yes G1:rTMS G2: Sham[Q60] Baseline n Observed Baseline: G1: 86 G2: 94 Observed at end of Phase I: G1: 78 G2: 88	stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient Adequate information Yes

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Baseline score, mean (SD) G1: 41.0 (9.3) G2: 40.1 (9.8) Endpoint score, mean (SD) Observed at 3 weeks G1: 32.56 (15.40) G2: 36.70 (13.91) G1: vs. G2, 95% CI, Cohen d, p-value: -10.04 to -2.62, -0.66, p = 0.001 Change, mean (SD) Observed at 3 weeks G1: -8.42(NR) G2: -3.37 (NR) Responders, n NR Remitters, n NR Other NA CGI-S Yes G1: rTMS G2: Sham Baseline n Observed at baseline: G1: 90 G2: 98	*Attrition* Overall, % All attrition calculations based on mITT 10.5% At end of treatment, % G1: 12 G2: 9 At end of followup, % G1: NA G2: NA Withdrawals due to efficacy, % G1: NR G2: NR Withdrawals due to adverse events, % G1: 5.4 G2: 0 Other *Adherence/ compliance* Adherence Fully Adherent n= 120 G1: n = 57 G2: n = 63

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Observed at end of Phase I: G1: 82 G2: 90 Baseline score, mean (SD) G1: 4.62 (0.70) G2: 4.63 (0.69) Endpoint score, mean (SD) Observed at 3 weeks G1: 3.96 (1.14) G2: 4.30 (0.87) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -0.68 to -0.09, -0.55, p = 0.01 Change, mean (SD) Observed at 3 weeks G1: -0.66 (NR) G2: -0.33(NR) Other NA	

Evidence Table 36. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Moore et al., 1997[43] *Country, setting* Scotland, University clinic, outpatients *Funding* Scottish Office, Home and Health Department *Research Objective* To compare CBT to additional meds in treatment of depression non-responsive to medication duringacute phase of study (results of Phase 1 reported elsewhere). *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers confirmed with ITT *N* 13 *Duration* 12 months *Interventions* G1: Medication G2: Cognitive Therapy *Medication Allowed* G1: Continued AD assigned in acute phase OR initiated another AD txt G2: Discontinued AD *Strategy* Mixed-between group differences *Parameters* • Medication dose within recognized therapeutic theshold • Psychotherapy • Type of therapy: Cognitive Therapy • Method: NR	*TRD definition* • Failure to respond to AD medication during 16 wk acute txt phase • Failure required to be in current episode *Tier 2* *Inclusion criteria* • HAM-D > 14 *Exclusion criteria* NA	*Baseline N* G1: 7 G2: 6 *Treatment Failure* Current episode failures, mean G1: NR Mean failed trials G1: NR *Polarity, %* Unipolar Overall: 100 *Age, mean yrs* Overall: 38 *Sex, % females* Overall: 62 *HAM-D 17* Baseline score, mean (SD) G1: 18.6 (3.3) G2: 18.3 (3.9) *BDI* Baseline score, mean (SD) G1: 30.6 (5.1) G2: 37.8 (5.1)	*Analyzed, n* G1: 4 G2: 5 *HAM-D 17* Endpoint score, mean (SD) 4 mos G1: 11.0 (2.3) G2: 19.8 (5.6) 8 mos G1: 6.6 (7.3) G2: 17.5 (1.9) 12 mos G1: 5.0 (5.7) G2: 14.3 (4.0) Completers, group by time, $P < 0.01$ ITT (LOCF), group by time, $P < 0.01$ Change, mean (SD) 4 month G1: -7.6 G2: +1.5 Partial responders, n Defined as HAM-D ≤ 14 G1: 5 G2: 2 $P = 0.17$ Full responders, n Defined as HAM-D ≤ 6 G1: 3	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 31% At end of treatment, % G1: 43 G2: 17 At end of follow-up, % G1: 43 G2: 17 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* NR

Evidence Table 36. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Number of sessions/week: min. 3/wk for 4wks and then 2/wk for 4wks and 1/wk for 4wks • Total number of sessions: NR			G2: 0 *P* = NR *BDI* Endpoint score, mean (SD) 4 mos. G1: 22.2 (5.9) G2: 41.5 (5.8) 8 mos. G1: 9.2 (8.3) G2: 34.3 (12.0) 12 mos. G1: 10.8 (12.2) G2: 35.8 (12.6) Group by time, *P* = 0.05 ITT (LOCF), group by time, *P* < 0.05 Change, mean (SD) At 4 months G1: -8.4 G2: +3.7 Partial responders, n Defined as BDI ≤ 16 G1: 4 G2: 0 *P* < 0.05 Full responders, n Defined as BDI ≤ 9 G1: 3 G2: 0 *P* = NR	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Harley, 2008[36] *Country, setting* United States, university clinics, outpatient psychiatric *Funding* Kaplan Fellowship Award Grant through Harvard Medical School *Research Objective* To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 24 *Duration* Primary outcome after 16 weeks of active txt Follow-up: 6 months *Interventions* G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control *Medications Allowed* Patients continued antidepressant therapy *Strategy* Augmentation *Parameters* • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1	*TRD definition* • 1+ failed medications (6+ weeks at "standard effective dose") • Not required or not specified to be in current episode *Tier 2* *Inclusion criteria* • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study. *Exclusion criteria* • Borderline personaliy disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.	*Baseline N* G1: 13 G2: 11 *Treatment Failure* Mean failed trials NR *Polarity, %* MDD *Overall:* 100 *Age, mean yrs* Overall: 41.8 *Sex, % females* Overall: 75 *Race, % white* Overall: 83 *HAM-D 17* Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) *P* = NS BDI Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) *P* = NS	*HAM-D 17* Analyzed n G1: 10 G2: 9 Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23) Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78 *P* < 0.05 Remitters, n Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) *P* = NR BDI Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30)	*Quality of Life Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT*) Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24) Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69) Change, mean (SD) G1: -1.3 G2: -0.33 *P* = NS *Social Adjustment Scale-Self-Report (SAS-SR) work subscale* Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Total number of sessions:16 G2: Wait list	• Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience.		Change, mean (SD) G1: -12.80 G2: -1.55 *P* < 0.01	Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 *P* < 0.05 *Adverse Events* NR *MMSE* NR *Attrition* Overall, %: 21 At end of treatment, % G1:23 G2:18 At end of follow-up, % G1:20 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0 Withdrawals due to adverse events, % 0

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem prevented second from continuing. *Adherence/ compliance* Compliance Participants completed a weekly check-in form asking about medication compliance over preceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had forgotten a medication dose between 1 to 4 times in previous month.

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Paykel, 1999[38] Scott, 2000[59] Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219. *Country, setting* UK, outpatient *Funding* Medical Research Council, London, England and a grant fromOxford and Anglia Region *Research Objective* To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintainance treatment with antidepressants. *Quality Rating* Good	*Study design* RCT *Type of analysis* ITT *N* 158 *Duration* Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks. *Interventions* G1: Clinical management Only G2: CT plus Clinical Management *Medications allowed* Continued on current medications with dose adjustments allowed *Strategy* Augmention *Parameters* Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual	*TRD definition* • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months. • Failure required to be in the current episode *Tier 2* *Inclusion criteria* • Unipolar depression, • aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression withinlast 18 months but not inlast 2 months, and	*Treatment Failure* Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar 100% 100% *Age, mean yrs* G1: 43.2 (11.2) G2: 43.5 (9.8) *Sex, % females* G1: 53% G2: 46% *HAM-D 17* Baseline n G1: 78 G2: 80 Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7) BDI Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)	HAM-D 17 G1: Clinical Management only G2: CT plus Clinical Management Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2) Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7) Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3) Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 *P* = NS Follow-up at 44 weeks G1: - 3.0 G2: -4.5 Follow-up at 68 weeks G1: -5.0 G2: -4.9 Responders, n NR	*Quality of Life* NR *Adverse Events* NR *Attrition* Overall, % 20% did not adhere to protocol through to study end or relapse point At end of treatment, % G1: 4 G2: 14 At end of follow-up, % G1: 12 G2: 10 Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR *Adherence/ compliance* Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Number of sessions/week: 1.25/wk • Total number of sessions: 16	• Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at leastprevious 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. *Exclusion criteria* • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage,		Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45)) BDI Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6), Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3) Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7) Change, mean (SD) At week 20 G1: -6.24 G2: -8.44 Responders, n NR Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%)	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		• any other primary Axis I disorder attime ofindex illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions.		Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36) Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93). Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219: Relapse was defined as: (1) meetingDSM-III criteria for major depressive disorder for	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms duringfollow-up phase between 2 successive ratings 2 months apart, reaching a score onHAM-D 17 of at least 13 on both occassions and a level of distress or dysfunction for whichthe withholding of additional active treatment was no longer justified	

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Hansen, 2010[6] Hansen *Country, setting* Denmark University Hospital Inpatient Psychiatric *Funding* Danish Council for Medical Research; Einar Geert-Jorgensen and Wife Ellen Geert-Jorgensen Research Foundation; Boutcher Worzner and wife Inger Worzner grant; the Aarhus University Foundation for Researhc in Mental Disease; the Foundation of Psychiatric Research *Research Objective* To compare the antidepressant efficacy and adverse effects of right prefrontal low-frequency rTMS with that of ECT. *Quality Rating* Fair - KQ1 KQ4?	*Study design* RCT *Type of analysis* ITT PP *N* 60 *Duration* Active treatment: 3 wks HAMD and UKU assessed at baseline and weekly intervals w/in 24 hrs of treatment Follow-up treatment: 7 wks (total duration) HAMD and UKU assessed at wk 5 and wk 7 *Interventions* ECT rTMS G1: rTMS G2: ECT *Medications Allowed* Continued current antidepressant medication; discontinued antiepileptics prescribed as mood stabilizers, benzodiazepines	*TRD definition* • Patients referred for ECT *Tier 3* *Inclusion criteria* • 18-80 yo; HAMD-17 total score of ≥ 20 and/or subscale score of ≥ 9; right-handed; ICD-10 diagnosis of moderate to severe depression; DSM-IV diagnosis of MDD; unipolar or bipolar *Exclusion criteria* • Organic brain damage; personal/family history of epileptic seizures, metallic objects in the chest or brain as a result of surgery; cardia pacemakers; somatic diseases associated w/ brain dysfunction; pregnancy; use of coercive measures; suicidal risk of severe degree; severe agitation; delirium; alcohol or drug dependence.	*Subgroups* No Subgroups *Baseline n* G1: 30 G2: 30 *Treatment Failure* Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR *Polarity, %* Unipolar G1: 86.7 G2: 86.7 Bipolar I G1: 13.3 G2: 13.3 Bipolar II G1: NR G2: NR	*HAM-D (Insert #)* Yes HAM-D17 G1: rTMS G2: ECT Endpoint score, mean (SD) Week 3 G1: NR Baseline - wk3 reduction, p <0.001 G2: NR Baseline - wk3 reduction, p <0.001 Week 3-7 G1: NR wk3 - wk7 reduction, p <0.001 G2: NR wk3 - wk7 reduction, p = 0.78 Week 7 G1: NR Baseline - wk 7 reduction, p < 0.001 G2: NR Baseline - wk 7 reduction, p < 0.001 Change, mean (SD) G1: NR G2: NR Responders, n Response Rate Difference Week 3, Rate (95% CI):	*Quality of Life* No *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % G1: 0 G2: 0 Dizziness, % NR Headache, % NR Insomnia, % NR Post op complications, % NR Somnolence, % Signficantly > decline in fatigue score in the ECT group (score NR)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	tapered off, low dose zopiclone or zopidem if needed for sleep *Strategy* Augment or add-on strategy *Parameters* G1: Location: Right DLPFC Frequency: 1 Hz Intensity: 110% MT Trains: 2 60s trains Intertrain interval: 180 s Number of session: 15 total (1 per week day for 3 weeks) G2: Location: Unilaterally over the right hemisphere Intensity: Recorded seizure duration ≥ 25 seconds; If between 15-25 seconds next treatment carried out with 50% higher stimulus intensity; If < 15 seconds then followed by restimulation. Number of session: 9 total (3 sessions weekly)		*Patient Characteristics* *Age, mean yrs* Median (range) G1: 46 (14-38) G2: 52 (29-79) p = 0.16 *Sex, % females* G1: 76.7 G2: 63.3 *Race, % white* G1: NR G2: NR *Not Specified, %* G1: NR G2: NR *Right handed, %* G1: 100 G2: 100 *Groups similar at baseline* Yes *HAM-D 17* Baseline score, mean (SD) Median (Range): G1: 24 (14-38) G2: 24 (16-34) G1: vs. G2: p = 0.68	G1: 0.20 (0.08-0.39) G2: 0.57 (0.37-0.75) G1: vs. G2 rate difference: 0.37 (0.14-0.59), p = 0.003 Week 7, Rate (95%CI): G1: 0.43 (0.25-0.63) G2: 0.60 (0.41-0.77) G1: vs. G2 rate differenc: 0.17 (-0.08, 0.42), p = 0.200 Remitters, n Remission Rate Difference Week 3 Rate (95% CI): G1: 0.27 (0.12 - 0.46) G2: 0.53 (0.34 - 0.72) G1: vs. G2 rate difference: 0.26 (0.03 - 0.51), p = 0.035 Week 7 Rate (95% CI): G1: 0.40 (0.23 - 0.59) G2: 0.57 (0.37 - 0.75) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200 Other Remission: HAMD-17 ≤ 12	Suicidality, % NR Additional Comments NR "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale. *Neuropsychological or executive functioning* Yes

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Response: ≥ 50% reduction in HAMD-17	Measures, Results Logical Memory – Immediate recall Baseline, Mean (SD): G1: 10.8 (4.4) G2: 10.0 (5.1) After Treatment G1: 8.8 (3.8) G2: 9.6 (5.1) Logical Memory – Delayed recall Baseline, Mean (SD): G1: 7.6 (5.4) G2: 7.46 (5.5) After Treatment G1: 7.2 (3.7) G2: 6.8 (5.8) Verbal Learning – Total Baseline, Mean (SD) G1: 8.2 (1.7) G2: 8.4 (2.1) After Treatment G1: 8.1 (2.0) G2: 7.9 (1.5) Verbal Learning – delayed recall Baseline, Mean (SD) G1: 5.9 (2.3) G2: 5.5 (2.0) After Treatment G1: 6.0 (2.6) G2: 4.8 (3.1) Rey Complex Figure – copy Baseline, Mean (SD) G1: 32.9 (4.2) G2: 29.7 (7.4)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					After Treatment G1: 33.6 (2.2) G2: 29.2 (6.8) Rey Complex Figure – delayed recall Baseline, Mean (SD) G1: 16.0 (6.2) G2: 13.9 (7.2) After Treatment G1: 25.6 (7.4) G2: 13.1 (9.4) G1: vs. G2, p <0.01 Within groups, p <0.01 Trail-Making Test A Baseline, Mean (SD) G1: 65.7 (35.5) G2: 64.7 (23.5) After Treatment G1: 60.6 (39.4) G2: 65.9 (34.0) Trail-Making Test B Baseline, Mean (SD) G1: 147.8 (64.4) G2: 131.3 (50.1) After Treatment G1: 131.0 (68.0) G2: 107.8 (36.0) SDMT Baseline, Mean (SD) G1: 29.9 (12.0) G2: 29.3 (13.7) After Treatment G1: 34.0 (12.6) G2: 31.1 (14.0) Verbal Fluency – letter S

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Baseline, Mean (S) G1: 10.4 (3.8) G2: 11.6 (7.3) After Treatment G1: 12.9 (5.6) G2: 10.3 (6.1) Verbal Fluency – animals Baseline, Mean (SD) G1: 18.4 (6.3) G2: 16.3 (4.5) After Treatment G1: 19.8 (6.2) G2: 14.11 (3.1) G1: vs. G2, $p < 0.05$ *Other* Yes "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale. Adequate information Yes *Attrition* Overall, % 30 At end of treatment, % G1: 33.3 G2: 26.7 At end of followup, % G1: NR G2: NR Withdrawals due to efficacy, % G1: NR G2: NR Withdrawals due to adverse events, % G1: NR G2: NR Other Withdrawal due to Discomfort at the stimulus site, % (n): G1: 16.7 (5) G2: 0 (0)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawal due to serious deterioration, % (n): G1: 10 (3) G2: 3 (1) Withdrawal due to somatic disease, % (n): G1: 3 (1) G2: 0 (0) Withdrawal due to Commotio cerebri, % (n): G1: 0 (0) G2: 3 (1) Withdrawal for unknown reasons, % (n): G1: 0 (0) G2: 3 (1) *Adherence/ compliance* None reported
Author, Year McLoughlin et al., 2007[7] Eranti et al., 2007[8] Knapp et al., 2008[9] *Country, setting* UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients *Funding* National Health Service Research and Development, National Coordinating Centre for	*Study design* RCT- pragmatic and single blinded (raters) *Type of analysis* m-ITT *N* 46 *Duration* Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months	*TRD definition* • All patients referred for ECT: • No failure required *Tier 3* *Inclusion criteria* • Right handed patients • more than 18 years old • refered for ECT due to major depressive episode *Exclusion criteria* • Inability to have rTMS because of metallic	*Treatment Failure* Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % *Age, mean yrs* G1: 63.6 G2: 68.3	*HAM-D 17* Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 *P* = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR *P* = 0.93	*Quality of Life* SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Health Technology Assessment (NCCHTA) (98/11/04); byGuy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression. *Research Objective* To assess clinical effectiveness of rTMS vs. ECT for treating major depressive episodes in patients referred for ECT *Quality Rating* Good	*Interventions* G1: ECT G2: rTMS *Medication Allowed* Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan) *Strategy* Augmentation *Parameters* rTMS • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15	implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.	*Sex, % females* G1: 67.7 G2: 72.7 *Right handed, %* Overall: 100% *HAM-D 17* Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0) *BDI:* Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)	Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 *P* = 0.017 Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Remitters, n HAM-D ≤ 8 End ot treatment G1: 13 (59.1%) G2: 4 (17.4%) *P* = 0.005 Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%) *only 12 ECT remitters followed after End of txt *BDI* Endpoint score, mean (SD) NR *P* = 0.01 effect size=0.9 Change, mean (SD) NR Group x time, *P* = 0.25	Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056) (QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. *Adverse Events* NR

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	ECT: • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5			Responders, n NR Remitters, n NR	*Neuropsychological or executive functioning* Predefined CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), *P* = 0.004 No significant differences for rest of CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory) MMSE Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 *P* < 0.08 No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects. **Attrition** Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0 At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Adherence/ compliance NR
Author, Year O'Connor, 2003[64] *Country, setting* United States, University Hospital, inpatient vs. outpatient population not clearly reported *Funding* NIH/NIMH and a NARSAD grant *Research Objective* Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition *Quality Rating* Poor	*Study design* Observational *Type of analysis* Completers *N* 28 *Duration* • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt *Medications allowed* rTMS patients completed a washout of all psychotropic medications while ECT continued all medications *Strategy* Switch strategy for rTMS and augment or add-on strategy for ECT group *Interventions* G1: ECT G2: rTMS	*TRD definition* • Patients referred for ECT • AD failures not required *Tier 3* *Inclusion criteria* • Met criteria for MDD • HRSD > 18 *Exclusion criteria* • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent	*Treatment Failure* Mean failed trials NR *Polarity, %* 100% MDD *Age, mean yrs* G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2 *HAM-D* Baseline n Completers G1: 14 G2: 14 Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) *P* = 0.001 *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)	*HAM-D* Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5) Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time *P* < 0.01 Responders, n G1: NR G2: 0 Remitters, n G1: NR G2: 100% *Other* Validated measure Yes *Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest* Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)	*Quality of Life* *Adverse Events* NR *Neuropsychological or executive functioning* Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning) Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09) Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00) Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: *P* > 0.05

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Parameters ECT • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12, rTMS • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks			Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with2 week follow-up results (*P* > 0.05) No significant interaction between treatment sessions and groups with respect to LN (*P* > 0.05)	G2: 44.07 (10.43) RAVLT, Acquisition, mean (SD) Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09). End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) *P* < 0.01. Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) *P* > 0.05. RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD) Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08) End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80) Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07). Transient News Events Test (TNET-measure of retrograde memory)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12) Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33) Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12) Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$. Cognitive function/memory impairment reported as primary outcome measures. *MMSE* NR *Attrition* Overall, % No attrition

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 *Adherence/ compliance* NR

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Bortolomasi et al., 2006[34] *Country, setting* Italy, single center, inpatient vs. outpatient NR *Funding* Not reported *Research Objective* To investigate outcome of depressed patients treated for 1 month with high frequency rTMS onleft frontal lobe at long time periods *Quality Rating* Fair	*Study design* RCT *Type of analysis* Cannot tell, all reported patients included in analysis *N* 19 *Duration* Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article *Interventions* G1: rTMS G2: Sham *Medications allowed* Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry) *Strategy* Augmentation Allowed to continue on failed SSRIs (63.2%)	*TRD definition* • Drug resistance (not defined) • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations *Exclusion criteria* • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps	*Treatment Failure* Mean failed trials NR *Polarity, %* Unipolar G1: 83.3 G2: 85.7 Bipolar G1: 16.7 G2: 14.3 *Age, mean yrs* G1: range 45-56 G2: range 44-53 Overall: 55.6 *Sex, % females* G1: 58 G2: 57 *Race, % white* NR *Right handed, %* Overall: 100 Groups similar at baseline Yes	*HAM-D 24* Endpoint score, mean (SD) At week 1 G1: 11.33 G2: 18.29 At week 4 G1: 11.42 G2: 19.14 At week 12 NR Change, mean (SD) At week 1 G1: -13.84 G2: NR *P* = NR, significant Group x time at wk 2 and 4, *P* < 0.05 At week 4 G1: -13.75 G2: NR At week 12 NR IG1: rTMS G2: Sham Baseline n G1: 12 G2: 7	*Quality of Life* NR *Adverse Events* No adverse effects were reported in either group, except for mild cephalgia by three patients treated with anti-inflammatory drugs Headache, % 3 patients reported mild headaches after treatment All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep. 3 patients reported mild headaches after treatment *Attrition* *Adherence/ compliance* NR

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	and TCAs (26.3%), No meds (5.3%) *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil Sham • Stimulation coil was placed perpendicular tothe scalp surface without direct contact. Coil position was fixed for all TMS sessions, and stimulation at this site evoked minimal motor activity		*Tier* *HAM-D 24* Baseline n G1: 12 G2: 7 Baseline score, mean (SD) G1: 25.17 G2: NR	Baseline score, mean (SD) G1: 25.42 G2: NR Endpoint score, mean (SD) At week 1 G1: 12.25 G2: 22.43 At week 4 G1: 11.67 G2: 24.57 Change, mean (SD) At week 1 G1: 13.17G2: NR At week 4 G1: 13.75 G2: NR	

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year George et al., 1997[35] *Country, setting* USA, outpatient setting *Funding* NARSAD, Ted and Vada Stlanley Foundation *Research Objective* To test hypothesis: daily left prefrontal rTMS has antidepressant effects *Quality Rating* Fair	*Study design* RCT, crossover *Type of analysis* ITT *N* 12 *Duration* 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt *Interventions* G1: rTMS G2: sham stimulation *Medications Allowed* ADs tapered for 9, 3 partial responders continued their medication *Strategy* Mixed-within group differences *Parameters* rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2	*TRD definition* • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode *Tier 3* *Inclusion criteria* • DSM-IV criteria for current MDD • right-handed *Exclusion criteria* • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma	*Treatment Failure* Number of previous AD medications Overall: 13.4 *Polarity, %* Unipolar Overall: 91.7 Bipolar II Overall: 8.3 *Age, mean yrs* Overall: 41.8 (12.4) *Sex, % females* Overall: 91.7 *Right handed, %* Overall: 100 *HAM-D 21* Baseline n G1: 12 G2: 12 Baseline score, mean (SD) Overall: 28.5 (4.2)	*HAM-D 21* G1: rTMS G2: sham stimulation Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 *P* < 0.03	*Quality of Life* NR *Adverse Events* Headache, % G1: 4/12 G2: NR Suicidality, % G1: 0 G2: Sham: 1/12 Seizures: None Unexpected side effects: None Headaches NR by active v. sham Memory or Attention: None *Attrition* Overall: 0 *Adherence/ compliance* N

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Inter-train interval: NR • Pulses per session: • Total number of sessions: 5/wk for a total of 20 per patient Sham: • Same as above but angled at 45 degrees from skull				

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Jorge et al., 2008[65] Experiment 1 *Country, setting* USA, university hospital, outpatients and inpatients *Funding* NIMH *Research Objective* To assess efficacy and safety of rTMS to treat vascular depression *Quality Rating* Fair	*Study design* RCT *Type of analysis* m-ITT *N* 30 *Duration* 3 weeks *Interventions* G1: rTMS G2: Sham *Medications Allowed* None, all antidepressants discontinued *Parameters* rTMS • Location of stimuli Left DLPC • Frequency 10 Hz • Intensity motor threshold. 110% • Pulses per session - 20 trains per day, seperated by 1 minute pauses total 12000 pulses • Number of sessions 10 in 10 days	*TRD definition* • 1+ failed trials at an adequate dose • Required to be in current episode Tier 2 *Inclusion criteria* • Onset of major depressive disorder (as diagnosed by DSM-IV criteria) at age 50 years or older • history of subcortical stroke and/or at least 3 offollowing cardiovascular risk factors: arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking *Exclusion criteria* • Severe heart or respiratory failure, renal or hepatic failure, oroccurrence of an ongoing neoplastic process, neurodegenerative disorders such as idiopathic Parkinson disease or probable Alzheimer disease	*Subgroups* Age 50+ *Baseline N* G1: 15 G2: 15 *Treatment Failure* Mean failed trials NR *Polarity, %* All pts met criteria for MDD in current episode 20% only met criteria for minor depression at study entry *Age, mean yrs* G1: 62.9 G2: 66.1 *Sex, % females* G1: 40 G2: 53 *HAM-D Baseline score, mean (SD)* G1: 19.5 (5.8) G2: 19.9 (5.4)	*HAM-D 17* Endpoint score, mean (SD) NR Change, mean (SD) G1: 33.1% G2: 13.6% *P* = 0.04 Responders, n G1: 5 (33.3%) G2: 1 (6.7%) *P* = 0.08 Remitters, n HAM-D17< 8 and did not meet criteria for major or minor depression G1: 2 (13.3%) G2: 1 (6.7%) *P* = 0.5	*Quality of Life* NR *Adverse Events* Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % NR Dizziness, % NR Headache, % G1: 33 G2: 27 Insomnia, % NR Post op complications, % NR Somnolence, % NR Suicidality, % NR

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham stimulation performed using a specially designed coil that looks exactly likestandard stimulating coil but generates a small localized field that drops off very fast, producing a scalp sensation without actual cortical stimulation *Strategy* Switch	• patients with clinical evidence of dementia, actively suicidal, prominent psychotic features, or with comorbid alcohol or other drug abuse, • prior occurrence of induced seizures, major head trauma, and a history of epilepsy, metal inskull, cranial cavity, or brain parenchyma, • cardiac pacemaker, an implanted defibrillator, or a medication pump.			Additional Comments TCD-12K vs. Sham Local pain 7 vs. 7 Local discomfort 27 vs. 33 Anxiety 13 vs. 0 "There were no significant differences betweenactive and sham stimulation groups infrequency of headaches or local discomfort. As expected, none ofpatients experienced a seizure. In addition, headaches were mild and responded in all cases to low doses of common analgesics." • Local pain 1 (7) vs. 1 (7) • Headaches 5 (33) vs. 4 (27) • Local discomfort 4 (27) vs. 5 (33) • Anxiety 2 (13) vs. 0 *Neuropsychological or executive functioning* Yes Measures, Results Variable Stimulation Group, Mean (SD) Scores

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					P Value TCD-12K vs. Sham / TCD-18K vs. Sham Baseline values MMSE score 28.1 (1.6) vs. 26.9 (2.8) / 28.2 (1.4) vs. 28.6 (1.7) *P* = 0.61 RAVLT trials 1-5, score 42.1 (11.3) vs. 36.2 (12.4) / 41.7 (10.1) vs. 44.2 (9.6) *P* = 0.34 RAVLT delayed recall, score 7.6 (4.1) vs. 5.4 (2.4) / 7.5 (3.8) vs. 8.2 (3.3) *P* = 0.16 Trail Making Test B, s 124.8 (67.6) vs. 117.0 (58.7) / 99.5 (59.4) vs. 106.8 (63.0) *P* = 0.24 Stroop Color and Word Test, interference 29.7 (8.3) vs. 29.4 (11.7) / 33.5 (9.2) vs. 30.3 (10.0) *P* = 0.46 COWAT score 38.5 (14.0) vs. 27.7 (9.9) / 35.3 (11.4) vs. 39.6 (12.9) *P* = 0.08 Compared with sham stimulation, active rTMS at TCD-12K and TCD-18K was not associated with significant changes in ADLs as measured byFunctional Independence Measure

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					or in most neuropsychological tests assessing memory and executive functions. However, after controlling for baseline Trail Making Test B time, patients receiving active rTMS had significantly decreased (ie, improved) Trail Making Test B times compared with patients receiving sham stimulation, forTCD-12K group (F1=7.7; *P* = 0.01) and TCD-18K group (F1=4.9; *P* = 0.03). No significant differences in Trail Making Test B times between responders and nonresponders, suggesting this effect was independent of mood. Predefined No *MMSE* Baseline n G1: 15 G2: 15

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Baseline score, mean (SD) G1: 28.1 (1.6) G2: 26.9 (2.8) Endpoint score, mean (SD) NR Change, mean (SD) NR *Other* "There were no significant differences betweenactive and sham stimulation groups infrequency of headaches or local discomfort. As expected, none of patients experienced a seizure. In addition, headaches were mild and responded in all cases to low doses of common analgesics." Local pain 1 (7) vs. 1 (7) Headaches 5 (33) vs. 4 (27) Local discomfort 4 (27) vs. 5 (33) Anxiety 2 (13) vs. 0 Adequate information No

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % • 5 dropped out before first stimulation = 5% • Did not report if it was from experiment 1 or 2 • No reported attrition after first stimulation. At end of treatment, % 0 At end of followup, % 0 Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 Other 5 patients withdrew before stimulation began *Adherence/ compliance* NR

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Jorge et al., 2004[66] *Country, setting* USA, single center, outpatients *Funding* Charles A Dana Foundation Grant *Research Objective* To test hypothesis - high frequency rTMS ofleft dorsolateral prefrontal cortex would produce a significant reduction of depressive symptoms without affecting cognitive status of patients *Quality Rating* Fair	*Study design* RCT *Type of analysis* ITT *N* 20 *Duration* Active: 2 weeks treatment with primary outcomes assessed at 1 week post rTMS txt. *Interventions* G1: rTMS G2: Sham *Medications Allowed* All AD tapered. No other drugs reported *Strategy* Switch *Parameters* rTMS • Location of stimuli LDLPFC • Frequency 10 Hz • Intensity motor threshold. 110% • Pulses per session - 1600 (32 trains) • Number of sessions 10 over 2 weeks	*TRD definition* • 2+ failed adequate trials (adequacy defined by ATHF) • Not required or not specified to be in current episode *Tier 1* *Inclusion criteria* • Patients that had had a stroke and suffered from depression *Exclusion criteria* • Presence of severe systemic disease or an ongoing neoplasia • Neurodegenerative disorders such as Parkinson disease or Alzheimer disease • Clinical evidence of dementia (MMSE scores less than 23) aphasic patients with severe language comprehension deficits actively suicidal or who presented with prominent psychotic features or a bipolar course • Evidence of alcohol or drug abuse during past 12 months	*Subgroups* Stroke induced depression *Treatment Failure* Mean failed trials, n (SD) G1: 3.8 G2: 3.8 *Polarity, %* 100% diagnosis of depression due to stroke 85% MDD 15% Minor Depression *Age, mean yrs* G1: 63.1 G2: 66.5 *Sex, % females* G1: 40 G2: 50 *HAM-D 17* Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 20.1 (6.7) G2: 20.8 (6.0)	*HAM-D 17* Endpoint score, mean (SD) G1: 12.8 G2: NR Change, mean % At week 3 G1: -38% (-7.3 pts) G2: -13% *P* < 0.006 Responders, n G1: 3 (30%) G2: 0 (0%) *P* = NS Remitters, n G1: 1 (10%) G2: 0 (0%) *P* = NS	*Quality of Life* NR *Adverse Events* Overall, % G1: NR Amnesia, % G1: NR Cardiovascular adverse events, % G1: NR Cognitive impairment, % G1: NR Dizziness, % G1: NR Headache, % G1: 30% Insomnia, % G1: 5% Post op complications, % G1: NR Somnolence, % G1: NR Suicidality, % G1: NR • Transient headaches (six patients) relieved with low doses of

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		• Prior occurrence of induced seizures, major head trauma • History of idiopathic epilepsy; metal in skull, cranial cavity, or brain parenchyma • Cardiac pacemaker, an implanted defibrillator, or intracardiac lines			acetaminophen, local discomfort at site of stimulation usually produced by tightness of stimulation cap (five patients), and an exacerbation of initial insomnia observed in one patient • No significant differences infrequency of adverse events betweenactive andsham rTMS groups • No patients with seizures or propagation of cortical excitability toipsilateral motor cortex *Neuropsychological or executive functioning* Yes Measures, Results • Neuropsychological variable at end point - mean (SD) • MMSE Scores 27.4 (3.0) vs. 26.5 (1.7) • RAVLT Scores, (delayed recall) 6.0 (3.2) vs. 5.2 (2.1) • COWAT Scores 36.0 (13.7) vs. 25.5 (6.5)

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					• Trail Making Test B 144.4 (72.7) vs. 146.8 (62.4) • BNT Scores 26.8 (3.4) vs. 24.8 (3.9) Predefined Yes MMSE Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 25.9 G2: 26.4 Endpoint score, mean (SD) G1: 27.4 (3.0) G2: 26.5 (1.7) Change, mean (SD) G1: +1.5 (1.3) G2: +0.1 (2.4) Other Mann–Whitney x-squared 1.8, df = 1, *P* = 0.18 Adequate information No

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Attrition Overall, % 0 At end of treatment, % 0 At end of follow up, % 0 Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 Other NR *Adherence/ compliance* NR

Evidence Table 41. KQ 6: Quality of life

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Harley, 2008[36] *Country, setting* United States, university clinics, outpatient psychiatric *Funding* Kaplan Fellowship Award Grant through Harvard Medical School *Research Objective* To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD *Quality Rating* Fair	*Study design* RCT *Type of analysis* Completers *N* 24 *Duration* Primary outcome after 16 weeks of active txt Follow up: 6 months *Interventions* G1: DBT-based skills training G2: Wait-list Control *Medications Allowed* Patients continued antidepressant therapy *Strategy* Augmentation *Parameters* • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1 • Total number of sessions:16 G2: Wait list	*TRD definition* • 1+ failed medications (6+ weeks at "standard effective dose") • Not required or not specified to be in current episode *Tier 2* *Inclusion criteria* • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study. *Exclusion criteria* • Borderline personaliy disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.	*Baseline N* G1: 13 G2: 11 *Treatment Failure* Mean failed trials NR *Polarity, %* MDD *Overall:* 100 *Age, mean yrs* Overall: 41.8 *Sex, % females* Overall: 75 *Race, % white* Overall: 83 *HAM-D 17* Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) *P* = NS *BDI* Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) *P* = NS	*HAM-D 17* Analyzed n G1: 10 G2: 9 Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23) Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78 *P* < 0.05 Remitters, n Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) *P* = NR *BDI* Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30) Change, mean (SD) G1: -12.80 G2: -1.55 *P* < 0.01	*Quality of Life Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT*) Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24) Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69) Change, mean (SD) G1: -1.3 G2: -0.33 *P* = NS *Social Adjustment Scale-Self-Report (SAS-SR) work subscale* Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		• Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience.			Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 *P* < 0.05 *Adverse Events* NR MMSE NR *Attrition* Overall, %: 21 At end of treatment, % G1:23 G2:18 At end of followup, % G1:20 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0 Withdrawals due to adverse events, % 0

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem preventedsecond from continuing. *Adherence/ compliance* Compliance Participants completed a weekly check-in form asking about medication compliance overpreceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					forgotten a medication dose between 1 to 4 times inprevious month.
Author, Year Fitzgerald et al., 2003[15] *Country, setting* Australia 2 general psychiatric services, outpatients *Funding* National Health and Medical Research Council and a grant fromStanley Medical Research Institute *Research Objective* To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group *Quality Rating* Good	*Study design* RCT *Type of analysis* ITT *N* 60 *Tier 1* *Duration* Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow up assessment conducted at 2 weeks post txt. *Interventions* G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham *Medications Allowed* 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood	*TRD definition* • Failed a minimum of 2 courses of antidepressant medications (6+ weeks) Not required or not specified to be in current episode *Inclusion criteria* • DSM-IV diagnosis of Major Depression (included bipolar depression) *Exclusion criteria* • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders	*Treatment Failure* Mean failed trials Overall (SD) 5.68 (3.40) Polarity, % Bipolar I G1: 5 G2: 5 G3: 20 *Age, mean yrs* G1: 42.2 G2: 45.55 G3: 49.15 *Sex, % females* G1: 40 G2: 35 G3: 55 *Right handed, %* G1: 90 G2: 100 G3: 85 *BDI* Baseline n G1: 20 G2: 20 G3: 20	*BDI* Endpoint score, mean (SD) At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7) Change, mean (SD) At 2 weeks G1:- 6.4 G2: -7.8 G3: -2.3 *P* = 0.03 *MADRS* Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5) Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) *P* = 0.004 G1: vs. G3, G2 vs. G3, *P* < 0.005	*Quality of Life* GAF Global Assessment of Functioning Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15) Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8) Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	stabilizers and antipsychotics *Strategy* Augmentation *Parameters* rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week		Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10) *MADRS* Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)	Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) *P* = 0.07 Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 *P* = NR *CGI* Endpoint score, mean (SD) NR *P* =.01	*Quality of Life* Overall group F56,2=2.6; *P* =.08; LFR-TMS vs sham: *P* = 0.03; and HFLTMS vs sham: *P* = 0.09 *Adverse Events* Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. • Although there was no difference in incidence of these adverse effects (*P* =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week				• Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: • One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium *Neuropsychological or executive functioning* • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions • Including all patients who underwent at least 1 type of active treatment, there was a significant

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					improvement in performance onverbal paired associates (t50=−7.3; *P* < 0.001), verbal fluency (t48=−3.8; *P* < 0.001), and digit span forwards (t48=−1.8; *P* = 0.003) subscales;Personal Semantic Memory Schedule (t50=−2.4; *P* = 0.02); andAutobiographical Memory Schedule (t50=−1.9; *P* = 0.05). • A similar pattern of improvements was seen for each oftreatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance oncognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores acrosssame times. MMSE NR

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Other *Attrition* Overall, % None in initial 2 week treatment phase At end of treatment, % 0 At end of followup, % NR But at least 28.3% did not continue on thru2nd 2 weeks Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 0 (1 during followup) G2: 0 (0 during followup) G3: 0 (0 during followup) Progression of patients through 2nd phase is very unclear *Adherence/ compliance* NR

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
Author, Year Rush et al., 2005[24] Carpenter et al., 2004[25] *Country, setting* US, multicente, outpatient psychiatric *Funding* Cyberonics, Inc. *Research Objective* To compare adjunctive VNS to sham in TRD patients *Quality Rating* Good	*Study design* RCT *Type of analysis* m-ITT/P*P* for efficacy, ITT for Aes *N* 235 *Duration* 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt *Interventions* G1: VNS G2: Sham *Medications allowed* pts allowed up to 5 antidepressants, mood stablizers, or other psychotropic medications *Strategy* Augmentation *Parameters* VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs • On/Off cycle parameters: 30 sec on and 5 min off	*TRD definition* • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode *Tier 1* *Inclusion criteria* • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium *Exclusion criteria* • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disoder, suicidality • risks related to surgical implantation	*Treatment Failure* Percent with 4-6 current episode failures G1: 46.5% G2: 40.0% *Polarity, %* Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6 Bipolar II G1: 6.3 G2: 5.5 *Age, mean yrs* G1: 47.0 G2: 45.9 *Sex, % females* G1: 59 G2: 66 *Race, % white* G1: 97 G2: 96 *HAM-D24* Baseline n G1: 119 G2: 116	*HAM-D24* N analyzed G1: 112 G2: 110 Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) *P* = 0.639 Responders, n G1: 17 (15.2%) G2: 11 (10.0%) *P* = 0.251 MADRS Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) *P* = 0.208 Responders, n G1: 17 (15.2) G2: 12 (0.0) *P* = 0.378 *IDS* Endpoint score, mean (SD) NR	*Quality of Life* Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2) Other Physical component between VNS and sham: *P* = 0.480, Mental Component between VNS and sham: *P* = 0.406

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	• Duration of treatment: Sham: • Device implanted but not turned on		Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2) MADRS Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3) IDS Baseline n G1: 112 (115 randomized) G2: 110 Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5) CGI-I Baseline n G1: 112 G2: 110	% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) *P* = 0.158 Responders, n G1: 19 (17) G2: 8 (7.3) *P* = 0.032 Remitters, n NR CGI-I Endpoint score, mean (SD) NR Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, *P* = 0.648	*Adverse Events* Overall, % NR Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:– • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%, • hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					patients, were cases of worsening depression requiring hospitalization Cardiac SAEs during implantation: 1.7% v 0% COSTART used to code reported events *Attrition* Overall, % 1.3 (3/235) At end of treatment, % G1: 2.6 G2: 0 At end of followup, % NR Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: 2.6 G2: 0 9 pts had a protocol violation post randomization *Adherence/ compliance* NR

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Appendix E. Abbreviations and Full Names of Diagnostic Scales and Other Instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range or mean of Scores	Improvement Denoted by
AMI	Autobiographical Memory Interview [1]	0–63	Increase
AMS	Autobiographical Memory Schedule[1]	0–9	Increase
BSRT	Buschke Selective Reminding Test - 12 free recall trials of a 12 item word list; on each trial the patient is reminded only of items forgotten on the previous trial. [2]	Varies	increase
CVLT	California Verbal Learning Test [3]	Varies- results are based on overall and differences	Increase on overall- decrease on change
CAMCOG	The cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly[4]	0–107	Increase
	Digit span forwards[5]	0–16	Increase
MMSE	Mini-mental state examination[6]	0–30	Increase
PSMS	Personal Semantic Memory Schedule[1]	0–86	Increase
RAVLT	Rey Auditory Verbal Learning Test - The RAVLT consists of 15 nouns read aloud for five consecutive trials with each trial followed by a free-recall trial. The total score is the total number of words recalled through the five trials.[7]	Varies	Increase
Stroop	The Stroop Color-Word Test[8]	Varies	Increase
TMT Part A and B	Trail making test Part A and B [9]	Mean - Part A 29 seconds Part B 75 seconds	Decrease
TNET	Transient News Events Test[10]	Varies	Increase

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Appendix F. Characteristics of Studies With Poor Internal Validity

To assess the quality (internal validity or risk of bias) of studies, we used predefined criteria based on those described in the AHRQ Methods Guide for Comparative Effectiveness Reviews (ratings: good, fair, poor). Elements of quality assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; overall and differential loss to follow-up; and the use of intention-to-treat analysis. We assessed observational studies based on the potential for selection bias (methods of selection of subjects and loss to followup), potential for measurement bias (equality, validity, and reliability of ascertainment of outcomes), adjustment for potential confounders, and statistical analysis.

In general terms, a "good" study has the least bias and results are considered to be valid. A "fair" study is susceptible to some bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting, large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To systematically rate studies, we designed and used a structured data abstraction form. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the accuracy, completeness, and consistency of the data abstraction, and independently rated the quality. If differences in quality ratings could not be resolved by discussion, a third senior reviewer was involved. The full research team met regularly during the article abstraction period to discuss global issues related to the data abstraction process. The following lists all the studies reviewed and rated as poor quality, with their design and primary reasons for the final rating.

Study	Design	Primary Reasons for Poor Quality Rating
Key Question 1a		
Gregory, 1985[1]	RCT	High potential for selection bias. Study does not report adequate information for assessment of bias, specifically regarding baseline characteristics. High rate of attrition. Study analysis was on completers only.
Grunhaus, 2000[2]	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy the other intervention group underwent and augmentative intervention strategy.
Wang, 2004[3]	RCT	High potential for selection bias. This article does not report adequate information for an assessment of bias, particularly regarding baseline differences and patient withdrawal from treatment. Inadequate reporting of randomization.
Key Question 1b		
Barker, 1987[4]	RCT	High potential for selection bias. Study does not report adequate information for an assessment of bias, particularly regarding baseline differences and patient withdrawal from treatment. Inadequate reporting of randomization techniques and reporting of statistical methodology. High attrition and modification of protocol.
Maes, 1996[5]	RCT	High potential for selection bias. No baseline information provided on TRD only group.

Study	Design	Primary Reasons for Poor Quality Rating
Sunderland, 1994[6]	RCT	High potential for measurement bias. Study does not report of any washout between crossovers. Study inadequately reports between group differences unable to asses differences on key outcomes (mean change, response, and remission).
Key Question 2		
Kauffmann, 2004[7]	RCT	High potential for measurement bias. Study does not provide numbers or methods for followup.
Key Question 3		
Grunhaus, 2000[2]	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy the other intervention group underwent and augmentative intervention strategy.
Key Question 4a		
Fitzgerald, 2006[8]	RCT	High potential for selection and measurement bias. Study poorly reports outcomes and to whom these outcomes are applicable.
Hansen, 2010[9]	RCT	High potential for selection bias. Analysis was performed on a subgroup of patients.
Frith, 1983; Frith, 1987[10,11]	RCT	High potential for selection bias. Analyses concerning cognition were done on an undefined subgroup.
Key Question 4b		
Bortolomasi, 2007[12]	RCT	High potential for selection bias and measurement bias. Poor reporting. Study does not provide how adverse events were solicited (i.e., spontaneous admission or solicited by provider). Does not specify whether reports of adverse events were reported by active or sham patients.
Fitzgerald, 2003[13]	RCT	High potential for selection bias. No systematic method of data collection.
Fitzgerald, 2006[8]	RCT	High potential for selection bias. No systematic method of data collection.
Grunhaus, 2003 [14]	RCT	High potential for selection bias. No systematic method of data collection.
Hansen, 2010[9]	RCT	High potential for selection bias. Analysis was performed on a subgroup of patients.
Holtzheimer, 2004[15]	RCT	High potential for selection and measurement bias. Does not provide how adverse events were solicited (i.e., spontaneous admission or solicited by provider).
Kauffmann, 2004[7]	RCT	High potential for measurement bias. Does not provide sufficient information to assess quality of data collection on adverse events.
Manes, 2001 [16]	RCT	High potential for selection, measurement, and/or confounding bias. No methodology reported.
Padberg, 1999[17]	RCT	High potential for selection bias. No method of collection reported, it is unclear if pts in sham condition were included in assessment.
Rosa, 2006 [18]	RCT	High potential for measurement bias. No systematic method of data collection.
Su, 2005[19]	RCT	High potential for selection bias. No systematic method of data collection.
Key Question 4d		
Grunhaus, 2000[2]	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy. The other intervention group underwent an augmentative intervention strategy.
Key Question 5		
Narushima, 2010[20]	RCT	High potential for selection bias. Inadequate reporting of randomization techniques and reporting of statistical methodology. High rate of differential and overall attrition
Takahashi, 2009[21]		High potential for measurement and selection bias. Study does not compare between interventions. Inadequate reporting of randomization techniques.
Key Question 6		
Wiles, 2008[22]	RCT	High potential for measurement bias. Scale used but outcomes not reported.

RCT = randomized controlled trial

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Appendix G. Articles by Database Searched

Cochrane Database = 82 articles (excluding duplicates)

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Appendix H: Studies Recommended for Inclusion by Peer and Public Reviewers

1. American Psychiatric Association. Committee on Electroconvulsive T, Weiner RD. The practice of electroconvulsive therapy: a task force report of the American Psychiatric Association. Washington, D.C.: American Psychiatric Association.

Rationale: This reference is a set of guidelines. Guidelines do not fit the inclusion criteria for appropriate publication types. The guidelines were not included in the analysis of this review.

2. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. J Clin Psychiatry. 2008 Mar;69(3):441-51.

Rationale: This reference was excluded due to a lack of comparison of interventions between groups. All patients participating in the open-label study receive the same intervention.

3. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. Journal of Clinical Psychopharmacology 2010 June;30(3):273-81.

Rationale: This reference was excluded for the present analysis due to a lack of comparison of interventions. The study analyzes outcome measures after 3, 12, and 24 months of vagal nerve stimulation.

4. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biological Psychiatry 2000 Feb;47(4):332-7.

Rationale: This study in included in the present analysis

5. Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness: Report to the Medical Research Council Br Med J 1965; 1:881-886

Rationale: This reference is from prior to the start date of our search criteria and it is not of a TRD population

6. Demitrack MA, Loo CK, Maixner DF, et al. Transcranial Magnetic Stimuatlin (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment. Society for Biological Psychiatry Annual Meeting New Research Sessions of the American Psychiatric Association Annual Meeting. Vancouver B.C. San Francisco, CA; 2009.

Rationale: This conference proceeding was included in our analysis as a companion article to O'Reardon, 2007.[1]

7. Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. Psychopharmacol Bull 2009 July;42(2):5-38.

Rationale: This article was excluded due to the wrong publication type. The study pooled two studies for the analysis. The current review reviewed both studies pooled for analysis for inclusion in this report. One article, O'Reardon, 2007[1] was included in our analysis. The second article, Avery, 2008[2] was excluded due to no comparison of interventions (see number 2 above).

8. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. Am J Psychiatry 2006:1161-72.

Rationale: This study was included in the Key Question 1b analysis (pharmaceutical interventions). Because it is comparing to pharmaceutical interventions it was only eligible to be included in Key Question 1.

9. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010 May;67(5):507-16.

Rationale: This study was included in the current analysis.

10. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005 Sep 1;58(5):364-73.

Rationale: This study was excluded from Key Question 2 (maintenance of response) analysis due to wrong study design (observational study). The protocol for this review states that only randomized controlled trials and meta-analyses are eligible study designs for this key question.

11. Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, et al. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. Journal of Clinical Psychiatry. 2004 Jun 2004;65(6):772-82.

Rationale: This study was excluded from analysis as it is not apparent that the population is treatment resistant. The article does not refer to the population as resistant or refractory, nor does it discuss prior treatment failures of the included population.

12. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. Brain Stimulation. Netherlands: Elsevier Science 2010:187-99.

Rationale: This article is included in the present analysis.

13. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 2008:222-32.

Rationale: This article is included in the present analysis.

14. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of acute tesponse to TMS in the treatment of major depression: relapse during a continuation pharmacotherapy extension study. Society for Biological Psychiatry Annual Meeting; 2007 May; San Diego, CA; 2007.

Rationale: This article is included in the present analysis.

15. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006:1337-44.

Rationale: This study was excluded for not meeting criteria for a treatment resistant population. The article states that only 42.7 percent of a portion of the population rated (using the ATHF) as having had at least one adequate failure. This indicates that 57.3 percent of this population did not have at least one treatment failure. The entire population, therefore, cannot be considered treatment-resistant by this review's definition.

16. Kozel FA, George MS, Simpson KN. Decision Analysis of Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy for Treatment of Nonpsychotic Severe Depression. CNS Spectrums. 2004 Jun 2004;9(6):476-82.

Rationale: This study was excluded from the current analysis due to reporting outcomes that are not of interest for this review. The study reports on an economic decision analysis.

17. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. JAMA 2008 Oct 1;300(13):1551-65.

Rationale: This meta-analysis was not included in the current analysis due to inclusion of the wrong population. It could not be determined that the included populations met the criteria of treatment-resistant depression.

18. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 2009 Jan;34(2):522-34.

Rationale: This study was excluded for wrong outcome. The study attempts to determine predictors of outcomes which is not an outcome of interest for this review.

19. Lisanby SH, Maddox JH, Prudic J, et al. The effects of electroconvulsive therapy on memory of autobiographical and public events. Arch Gen Psychiatry 2000 Jun;57(6):581-90.

Rationale: This study was excluded from the analysis. The study performs its analysis on right unilateral compared to bilateral electrode placement for electroconvulsive therapy. It also compares low versus high electrical dosage. Neither of these comparisons are comparisons of interest for this review.

20. Martis B, Alam D, Dowd SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin Neurophysiol 2003 Jun;114(6):1125-32.

Rationale: This article was excluded from this review due to no comparison. This article, although part of a larger randomized controlled trial, only reports on those persons receiving rTMS. The study does not report on any comparison intervention.

21. Nahas Z, Marangell LB, Husain MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 2005 Sep;66(9):1097-104.

Rationale: This article was excluded from this review due to no comparison. This study analyzes the outcomes from patients treated with vagal nerve stimulation. No other intervention is compared.

22. Nelson AL, Cohen JT, Greenberg D, et al. Much cheaper, almost as good: decrementally cost-effective medical innovation. Ann Intern Med 2009 Nov 3;151(9):662-7.

Rationale: This meta-analysis was excluded from the current analysis for wrong outcomes. The meta-analysis reviews cost-utility analyses which are not outcomes of interest for the current review.

23. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci USA 2003 Nov 25;100(24):14293-6.

Rationale: This study was excluded from the current analysis for including the wrong population. The identical sample used in this study was taken from Keller, 2000 [3] which was excluded from the current review due to wrong population. The population of the parent study and this subsequent study used as exclusion criteria "absence of a response to three previous adequate trials of at least two different classes of antidepressants or electroconvulsive therapy or to two previous adequate trials of empirical psychotherapy in the three years preceding the study; a serious, unstable medical condition; or a positive urine screen for drugs of abuse. Furthermore, out of the entire study population, 19.7 percent had received no prior treatment for depression.

24. Nierenberg AA, Fava M, Trivedi MH, et al. Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report. The American Journal of Psychiatry 2006 Sept;163(9):1519-30.

Rationale: This study was excluded from the current analysis do to wrong intervention. T3 is not an augmenter of interest for Key Question 1b (pharmaceutical) analysis.

25. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007:1208-16.

Rationale: This study is included in the current analysis. It is not included for Key Question 3 (symptom subtypes). Symptom subtypes represented by standard factor scores measured on the Hamilton Depression Rating Scale are not symptom subtypes of interest for this report.

26. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009 Dec;120(12):2008-39.

Rationale: This study was not included in the current analysis because it does not represent a publication type of interest. The reference is cited within the text of the current review.

27. Rumi DO, Gattaz WF, Rigonatti SP, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. Biol Psychiatry 2005 Jan 15;57(2):162-6.

Rationale: This study was not included in the current analysis due to inclusion of wrong population. The study makes no reference to the population as resistant or refractory, nor does it address prior treatment failure.

28. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biological Psychiatry 2005 Sep 2005;58(5):347-54.

Rationale: This study in included in the current analysis.

29. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1231-42.

Rationale: This study was not included for Key Question 1b (Pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.

30. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001 Mar 14;285(10):1299-307.

Rationale: This study was not included for Key Question 1b (pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.

31. Sackeim HA, Brannan SK, Rush AJ, et al. Durability of antidepressant response to vagus nerve stimulation (VNS). Int J Neuropsychopharmacol 2007 Dec;10(6):817-26.

Rationale: This study was not included in the current analysis because it does not contain a comparison of interest. The study analyzes outcomes after vagal nerve stimulation and compares outcomes between responders and non-responders.

32. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57(5):425-34.

Rationale: This study was not included in the current analysis because the analysis does not include a comparison of interest. The study compares right unilateral ECT at three different thresholds to bilateral ECT at one threshold. There is no other intervention comparison.

33. Sackeim HA, Prudic J, Fuller R, et al. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007 Jan;32(1):244-54.

Rationale: This study was not included in the current analysis because the analysis does not include a comparison. The study compares baseline and post-treatment outcomes after electroconvulsive therapy.

34. Simpson KN, Welch MJ, Kozel FA, et al. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv Ther 2009 Mar;26(3):346-68.

Rationale: This study was not included in the current analysis for reporting outcomes that were not of interest for the current review. The study performs cost-effective analyses. Please note the study is cited in the text of the review.

35. Tew JD, Jr., Mulsant BH, Haskett RF, et al. Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. Ann Clin Psychiatry 2007 Jan-Mar;19(1):1-4.

Rationale: This study was excluded for wrong comparison. In this continuation study which would have been considered for key question 2, the study only compares pharmacotherapy to treatment as usual which is not a comparison of interest for this key question.

36. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. Am J Psychiatry 2007:739-52.

Rationale: This study is included in the current analysis.

37. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1243-52.

Rationale: This study was excluded for wrong population. This study population did not meet the strict population criteria of Key Question 1b which required the entire population to have failed at least 2 prior treatments.

38. Williams N, Simpson AN, Simpson K, et al. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. Hum Psychopharmacol 2009 July;24(5):401-8.

Rationale: This meta-analysis was not included in this review because it included populations that are not treatment-resistant. The authors clearly stated that three of the studies excluded treatment-resistant depression and seven studies had no criteria pertaining to TRD.

39. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003 Mar 8;361(9360):799-808.

Rationale: Overall review excluded because populations were not all TRD, but we note that two of the studies from this SER are included in KQ1a.

References

1. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007:1208-16.

2. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. J Clin Psychiatry 2008 Mar;69(3):441-51.

3. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342(20):1462-70.