Number 6

Effective Health Care

Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

Executive Summary

Background

Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are atypical antipsychotics approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These drugs have been studied for off-label use in the following conditions: dementia and severe geriatric agitation, depression, obsessive-compulsive disorder, posttraumatic stress disorder, and personality disorders. The atypicals have also been studied for the management of Tourette's syndrome and autism in children. The purpose of this report is to review the scientific evidence on the safety and effectiveness of such off-label uses.

The Key Questions were:

Key Question 1. What are the leading off-label uses of atypical antipsychotics in the literature?

Key Question 2. What does the evidence show regarding the effectiveness of atypical antipsychotics for off-label indications, such as depression? How do atypical antipsychotic medications compare with other drugs for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses?

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics?

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

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Effective Health Care

Conclusions

Evidence on the efficacy of off-label use of atypical antipsychotics is summarized in Table A. Table B summarizes findings on adverse events and safety.

Leading off-label uses of atypical antipsychotics

- The most common off-label uses of atypical antipsychotics found in the literature were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. In October 2006, the FDA approved risperidone for the treatment of autism.

Effectiveness and comparison with other drugs

Dementia-agitation and behavioral disorders

- A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. The clinical benefits must be balanced against side effects and potential harms. See "Potential adverse effects and complications" section.
- Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found three studies of quetiapine; they were too dissimilar in their design and the outcomes studied to pool.
- A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo.
- We found no studies of ziprasidone for treatment of agitation and behavioral disorders in patients with dementia.
- Strength of evidence = moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.

Depression

- We identified seven trials where atypical antipsychotics were used to augment serotonin reuptake inhibitor (SRI) treatment in patients with initial poor response to therapy, two studies in patients with depression with psychotic features, and four trials in patients with depression with bipolar disorder.
- For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.
- In two trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined, as the trial lacked a fluoxetine-only comparison arm.
- For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies that compared atypical antipsychotics to conventional treatment.
- We found no studies of aripiprazole for depression.
- Strength of evidence = moderate strength of evidence that olanzapine, whether used as monotherapy or augmentation, does not improve outcomes at 8 weeks in SRI-resistant depression; low strength of evidence for all atypical antipsychotics for other depression indications due to small studies, inconsistent findings, or lack of comparisons to usual treatment.

Obsessive-compulsive disorder (OCD)

- We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment.
- Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics have a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy for patients who fail to adequately respond to SRI therapy. Overall, patients taking atypical antipsychotics were 2.66 times as likely to "respond" as placebo patients (95-percent confidence interval (CI): 1.75 to 4.03). Relative risk of "responding" was 2.74 (95-percent

CI: 1.50 to 5.01) for augmentation with quetiapine and 5.45 (95-percent CI: 1.73 to 17.20) for augmentation with risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.

- We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.
- Strength of evidence = moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.

Posttraumatic stress disorder (PTSD)

- We found four trials of risperidone and two trials of olanzapine of at least 6 weeks duration in patients with PTSD.
- There were three trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication.
- There were three trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.
- We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.
- Strength of evidence = low for risperidone and olanzapine for combat-related PTSD due to sparse data; very low for risperidone or olanzapine for treating non-combat-related PTSD.

Personality disorders

- We identified five trials of atypical antipsychotic medications as treatment for borderline personality disorder and one trial as treatment for schizotypal personality disorder.
- Three randomized controlled trials (RCTs), each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder.
- The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.
- Olanzapine caused significant weight gain in all studies.
- Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small 9-week trial.
- Aripiprazole was more effective than placebo for the treatment of borderline personality in one small 8-week trial.
- We found no studies of quetiapine or ziprasidone for personality disorders.
- Strength of evidence = very low due to small effects, small size of studies, and limitations of trial quality (e.g., high loss to followup).

Tourette's syndrome

- We found four trials of risperidone and one of ziprasidone for treatment of Tourette's syndrome.
- Risperidone was more effective than placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three remaining trials.
- The one available study of ziprasidone showed variable effectiveness compared to placebo.
- We found no studies of olanzapine, quetiapine, or aripiprazole for Tourette's syndrome.
- Strength of evidence = low for risperidone; very low for ziprasidone.

Autism

- Just before this report was published, the FDA approved risperidone for use in autism.
- Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. The first trial showed a greater effect for risperidone than placebo (57-percent decrease vs. 14-percent decrease in the irritability subscale of the Aberrant Behavior Checklist). In the second trial, more risperidone-treated than placebo-treated children improved on that subscale (65 percent vs. 31 percent).
- We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for this indication.
- Strength of evidence = low.

Population that would benefit most from atypical antipsychotics

- There was insufficient information to answer this question. It is included as a topic for future research.

Potential adverse effects and complications

- There is high-quality evidence that olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics. In two pooled RCTs of dementia patients, olanzapine users were 6.12 times more likely to report weight gain than placebo users. In a head-to-head trial of dementia patients, olanzapine users were 2.98 times more likely to gain weight than risperidone patients. In the CATIE trial, elderly patients with dementia who were treated with olanzapine, quetiapine, or risperidone averaged a monthly weight gain of 1.0, 0.7, and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month. Even greater weight gain relative to placebo has been reported in trials of non-elderly adults.
- In two pooled RCTs for depression with psychotic features, olanzapine patients were 2.59 times as likely as those taking conventional antipsychotics to report weight gain.
- In a recently published meta-analysis of 15 dementia treatment trials, death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics vs. 2.3 percent of patients randomized to receive placebo. The odds ratio for death was 1.54, with a 95-percent CI of 1.06 to 2.23. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. Recent data from the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network suggest that conventional antipsychotics are also associated with an increased risk of death in elderly patients with dementia, compared to placebo.
- In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.
- In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo (odds ratio (OR): 3.88; 95-percent CI: 1.49 to 11.91). This risk was equivalent to 1 additional stroke for every 31 patients treated in this patient population (i.e., number needed to harm of 31). The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone as in the placebo patients.
- In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.
- We pooled three aripiprazole trials and four risperidone trials that reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS (OR: 2.53 and 2.82, respectively) compared to placebo. The number needed to harm was 16 for aripiprazole and 13 for risperidone.
- Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, PTSD, or personality disorders (OR: 3.32; 95-percent CI: 1.12 to 13.41).
- In the CATIE trial, risperidone, quetiapine, and olanzapine were each more likely to cause sedation than placebo (15-24 percent vs. 5 percent), while olanzapine and risperidone were more likely to cause extrapyramidal signs than quetiapine or placebo (12 percent vs. 1-2 percent). Cognitive disturbance and psychotic symptoms were more common in olanzapine-treated patients than in the other groups (5 percent vs. 0-1 percent).
- There is insufficient evidence to compare atypical with conventional antipsychotics regarding EPS or tardive dyskinesia in patients with off-label indications.

- Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.
- Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.

Appropriate dose and time limit

- There was insufficient information to answer this question. It is a topic for future research.

Remaining Issues

More research about how to safely treat agitation in dementia is urgently needed. The CATIE-AD study has substantially added to our knowledge, but more information is still necessary. We make this statement based on the prevalence of the condition and uncertainty about the balance between risks and benefits in these patients. While the increased risk of death in elderly dementia patients treated with atypical antipsychotics was small, the demonstrable benefits in the RCTs were also small. Information is needed on how the risk compares to risks for other treatments.

An established framework for evaluating the relevance, generalizability, and applicability of research includes assessing the participation rate, intended target population, representativeness of the setting, and representativeness of the individuals, along with information about implementation and assessment of outcomes. As these data are reported rarely in the studies we reviewed, conclusions about applicability are necessarily weak. In many cases, enrollment criteria for these trials were highly selective (for example, requiring an open-label run-in period). Such highly selective criteria may increase the likelihood of benefit and decrease the likelihood of adverse events. At best, we judge these results to be only modestly applicable to the patients seen in typical office-based care.

With few exceptions, there is insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotic medications for any of the off-label indications, either vs. placebo or vs. active therapy.

More head-to-head trials comparing atypical antipsychotics are needed for off-label indications other than dementia.

Full Report

This executive summary is part of the following document: Shekelle P, Maglione M, Bagley S, Suttorp M, Mojica WA, Carter J, Rolon C, Hilton L, Zhou A, Chen S, Glassman P. Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics. Comparative Effectiveness Review No. 6. (Prepared by the Southern California/RAND Evidence-based Practice Center under Contract No. 290-02-003.) Rockville, MD: Agency for Healthcare Research and Quality. January 2007. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Table A. Summary of Evidence-Efficacy of Off-Label Use of Atypical Antipsychotics

Condition	Strength of evidence	Conclusion
Behavioral problems in dementia	Moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.	• A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. • Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found 3 studies of quetiapine; they were too dissimilar in their design and outcomes to pool. • A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo. • We found no studies of ziprasidone for agitation and behavioral disorders in elderly persons with dementia.
Specific categories of depression: a. Inadequate response to SRI b. With psychotic features c. With bipolar disorder	Moderate that olanzapine, whether used as monotherapy or to augment therapy, does not improve outcomes at 8 weeks in SRI-resistant depression; low for all atypical antipsychotics for other depression indications, due to small studies, inconsistent findings, or lack of comparisons to usual treatments.	• For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks. • In 2 trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined as the trial lacked a fluoxetine-only comparison arm. • For bipolar depression, olanzapine and quetiapine were superior to placebo in 1 study for each drug, but data are conflicting in 2 other studies that compared atypical antipsychotics to conventional therapy. • We found no studies of aripiprazole for depression.
Obsessive-compulsive disorder	Moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.	• We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment. • A moderate amount of evidence from 9 trials shows that these drugs have a clinically important beneficial effect when used as augmentation therapy for patients who failed to adequately respond to SRI therapy.

Table A. Summary of Evidence-Efficacy of Off-Label Use of Atypical Antipsychotics (continued)

Condition	Strength of evidence	Conclusion
Obsessive-compulsive disorder (continued)		• We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.
Posttraumatic stress disorder	Low for risperidone for combat-related PTSD due to sparse data; very low for risperidone and olanzapine for treating non-combat-related PTSD.	• We found four risperidone and two olanzapine trials of over 6 weeks for PTSD. • There were 3 trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. • We found 3 trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy. • We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.
Personality disorders	Very low due to small effects, small size of studies, and limitations of trial quality.	• 4 RCTs, each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder. • The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small. • Olanzapine caused significant weight gain in all studies. • Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in 1 small 9-week trial. • Aripiprazole was more effective than placebo for the treatment of borderline personality in 1 small 8-week trial.
Tourette's syndrome in children/adolescents	Low for risperidone; very low for ziprasidone.	• We found 4 trials of risperidone and 1 of ziprasidone for this condition. • The little evidence available is inconclusive about the efficacy of either drug. • We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.
Autism in children/Adolescents	Low for risperidone due to sparse data.	• Just before this report was published, the FDA approved risperidone for use in autism. • Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. • We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for autism.

Abbreviations: FDA = U.S. Food and Drug Administration; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SRI = serotonin reuptake inhibitor.

Table B. Summary of Adverse Event and Safety Findings Concerning Off-Label Use of Atypical Antipsychotics for Which There is Moderate or Strong Evidence

Side effect	Head-to-head trials	Active control trials	Placebo controlled trials
Mortality (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for atypical antipsychotics compared to placebo.
Cardiovascular (not including cerebrovascular accident)	Insufficient evidence of difference.	Insufficient evidence of difference.	Insufficient evidence of difference.
Cerebrovascular accident (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for risperidone and olanzapine compared to placebo.
Extrapyramidal symptoms	More common in olanzapine and risperidone than in quetiapine.	Insufficient evidence of difference.	More common in risperidone, olanzapine, aripiprazole, and ziprasidone than placebo, quetiapine insufficiently studied.
Neurological (fatigue, headaches, dizziness; excludes movement disorders)	Insufficient evidence of difference.	Insufficient evidence of difference.	More common in risperidone, olanzapine and aripiprazole than placebo; other drugs insufficiently studied.
Sedation	Insufficient evidence of difference.	More common in olanzapine than mood stabilizers.	More common in atypical antipsychotics than placebo.
Weight gain	More common in olanzapine than other atypical antipsychotics.	More common in olanzapine than conventional antipsychotics.	More common in olanzapine and risperidone than placebo; other drugs insufficiently studied.

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Comparative Effectiveness Review

Number 6

Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

This report is based on research conducted by the Southern California/RAND Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0003). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

Comparative Effectiveness Review

Number 6

Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

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

Contract No. 290-02-0003

Prepared by:
Southern California/RAND Evidence-based Practice Center

Investigators
Paul Shekelle, M.D., Ph.D.
Director
Margaret Maglione, M.P.P.
Project Manager/Policy Analyst
Steven Bagley, M.D., M.S.
Content Expert/Physician Reviewer
Marika Suttorp, M.S.
Statistician
Walter A. Mojica, M.D., M.P.H.
Physician Reviewer
Jason Carter, B.A.
Cony Rolón, B.A.
Literature Database Managers
Lara Hilton, B.A.
Programmer/Analyst
Annie Zhou, M.S.
Statistician
Susan Chen, B.A.
Staff Assistant
Peter Glassman, M.B., B.S., M.Sc.
Pharmacy Benefits Management Expert
Sydne Newberry, Ph.D.
Medical Editor

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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 State Children's Health Insurance Program (SCHIP).

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 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 strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

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

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

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Technical Expert Panel

Mark S. Bauer, M.D., Brown University, Providence Veterans Affairs Medical Center, Providence, RI

Barbara Curtis, R.N., M.S.N., Washington State Department of Corrections, Olympia, WA

Carol Eisen, L.A. County Department of Mental Health, Los Angeles, CA

Bruce Kagan, M.D., Ph.D., UCLA Psychiatry and Biobehavioral Science – Neuropsychiatric Institute, Los Angeles, CA

Jamie Mai, Pharm.D., Office of the Medical Director, Tumwater, WA

Alexander L. Miller, M.D., University of Texas, Department of Psychiatry, Health Science Center at San Antonio, San Antonio, TX

Adelaide S. Robb, M.D., Children's National Medical Center, Department of Psychiatry, Washington, DC

Charles Schulz, M.D., University of Minnesota, Department of Psychiatry, Minneapolis, MN

Sarah J. Spence, M.D., Ph.D., UCLA, Autism Evaluation Clinic, Los Angeles, CA

David Sultzer, M.D., UCLA and VA Greater L.A. Healthcare System, Department. of Psychiatry and Biobehavioral Sciences, Los Angeles, CA

AHRQ Contacts

Beth A. Collins-Sharp, Ph.D., R.N.
Director
Evidence-based Practice Center Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
Rockville, MD

Margaret Coopey, M.P.S., M.G.A., R.N.
Task Order Officer
Evidence-based Practice Center Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
Rockville, MD

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Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

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Background

Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are atypical antipsychotics approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These drugs have been studied for off-label use in the following conditions: dementia and severe geriatric agitation, depression, obsessive-compulsive disorder, posttraumatic stress disorder, and personality disorders. The atypicals have also been studied for the management of Tourette's syndrome and autism in children. The purpose of this report is to review the scientific evidence on the safety and effectiveness of such off-label uses.

The Key Questions were:

Key Question 1. What are the leading off-label uses of atypical antipsychotics in the literature?

Key Question 2. What does the evidence show regarding the effectiveness of atypical antipsychotics for off-label indications, such as depression? How do atypical antipsychotic medications compare with other drugs for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses?

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics?

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

Conclusions

Evidence on the efficacy of off-label use of atypical antipsychotics is summarized in Table A. Table B summarizes findings on adverse events and safety.

Leading off-label uses of atypical antipsychotics

- The most common off-label uses of atypical antipsychotics found in the literature were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. In October 2006, the FDA approved risperidone for the treatment of autism.

Effectiveness and comparison with other drugs

Dementia-agitation and behavioral disorders

- A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. The clinical benefits must be balanced against side effects and potential harms. See "Potential adverse effects and complications" section.

- Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found three studies of quetiapine; they were too dissimilar in their design and the outcomes studied to pool.

- A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo.

- We found no studies of ziprasidone for treatment of agitation and behavioral disorders in patients with dementia.

- Strength of evidence = moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.

Depression

- We identified seven trials where atypical antipsychotics were used to augment serotonin reuptake inhibitor (SRI) treatment in patients with initial poor response to therapy, two

studies in patients with depression with psychotic features, and four trials in patients with depression with bipolar disorder.

- For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.

- In two trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined, as the trial lacked a fluoxetine-only comparison arm.

- For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies that compared atypical antipsychotics to conventional treatment.

- We found no studies of aripiprazole for depression.

- Strength of evidence = moderate strength of evidence that olanzapine, whether used as monotherapy or augmentation, does not improve outcomes at 8 weeks in SRI-resistant depression; low strength of evidence for all atypical antipsychotics for other depression indications due to small studies, inconsistent findings, or lack of comparisons to usual treatment.

Obsessive-compulsive disorder (OCD)

- We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment.

- Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics have a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy for patients who fail to adequately respond to SRI therapy. Overall, patients taking atypical antipsychotics were 2.66 times as likely to "respond" as placebo patients (95-percent confidence interval (CI): 1.75 to 4.03). Relative risk of "responding" was 2.74 (95-percent CI: 1.50 to 5.01) for augmentation with quetiapine and 5.45 (95-percent CI: 1.73 to 17.20) for augmentation with risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.

- We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.

- Strength of evidence = moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.

Posttraumatic stress disorder (PTSD)

- We found four trials of risperidone and two trials of olanzapine of at least 6 weeks duration in patients with PTSD.

- There were three trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication.

- There were three trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.

- We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.

- Strength of evidence = low for risperidone and olanzapine for combat-related PTSD due to sparse data; very low for risperidone or olanzapine for treating non-combat-related PTSD.

Personality disorders

- We identified five trials of atypical antipsychotic medications as treatment for borderline personality disorder and one trial as treatment for schizotypal personality disorder.

- Three randomized controlled trials (RCTs), each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder.

- The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.

- Olanzapine caused significant weight gain in all studies.

- Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small 9-week trial.

- Aripiprazole was more effective than placebo for the treatment of borderline personality in one small 8-week trial.

- We found no studies of quetiapine or ziprasidone for personality disorders.

- Strength of evidence = very low due to small effects, small size of studies, and limitations of trial quality (e.g., high loss to followup).

Tourette's syndrome

- We found four trials of risperidone and one of ziprasidone for treatment of Tourette's syndrome.
- Risperidone was more effective than placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three remaining trials.
- The one available study of ziprasidone showed variable effectiveness compared to placebo.
- We found no studies of olanzapine, quetiapine, or aripiprazole for Tourette's syndrome.
- Strength of evidence = low for risperidone; very low for ziprasidone.

Autism

- Just before this report was published, the FDA approved risperidone for use in autism.
- Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. The first trial showed a greater effect for risperidone than placebo (57-percent decrease vs. 14-percent decrease in the irritability subscale of the Aberrant Behavior Checklist). In the second trial, more risperidone-treated than placebo-treated children improved on that subscale (65 percent vs. 31 percent).
- We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for this indication.
- Strength of evidence = low.

Population that would benefit most from atypical antipsychotics

- There was insufficient information to answer this question. It is included as a topic for future research.

Potential adverse effects and complications

- There is high-quality evidence that olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics. In two pooled RCTs of dementia patients, olanzapine users were 6.12 times more likely to report weight gain than placebo users. In a head-to-head trial of dementia patients, olanzapine users were 2.98 times more likely to gain weight than risperidone patients. In the CATIE trial, elderly patients with dementia who were treated

with olanzapine, quetiapine, or risperidone averaged a monthly weight gain of 1.0, 0.7, and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month. Even greater weight gain relative to placebo has been reported in trials of non-elderly adults.

- In two pooled RCTs for depression with psychotic features, olanzapine patients were 2.59 times as likely as those taking conventional antipsychotics to report weight gain.

- In a recently published meta-analysis of 15 dementia treatment trials, death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics vs. 2.3 percent of patients randomized to receive placebo. The odds ratio for death was 1.54, with a 95-percent CI of 1.06 to 2.23. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. Recent data from the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network suggest that conventional antipsychotics are also associated with an increased risk of death in elderly patients with dementia, compared to placebo.

- In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.

- In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo (odds ratio (OR): 3.88; 95-percent CI: 1.49 to 11.91). This risk was equivalent to 1 additional stroke for every 31 patients treated in this patient population (i.e., number needed to harm of 31). The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone as in the placebo patients.

- In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.

- We pooled three aripiprazole trials and four risperidone trials that reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS (OR: 2.53 and 2.82, respectively) compared to placebo. The number needed to harm was 16 for aripiprazole and 13 for risperidone.

- Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, PTSD, or personality disorders (OR: 3.32; 95-percent CI: 1.12 to 13.41).

- In the CATIE trial, risperidone, quetiapine, and olanzapine were each more likely to cause sedation than placebo (15-24 percent vs. 5 percent), while olanzapine and

risperidone were more likely to cause extrapyramidal signs than quetiapine or placebo (12 percent vs. 1-2 percent). Cognitive disturbance and psychotic symptoms were more common in olanzapine-treated patients than in the other groups (5 percent vs. 0-1 percent).

- There is insufficient evidence to compare atypical with conventional antipsychotics regarding EPS or tardive dyskinesia in patients with off-label indications.

- Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.

- Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.

Appropriate dose and time limit

- There was insufficient information to answer this question. It is a topic for future research.

Remaining Issues

More research about how to safely treat agitation in dementia is urgently needed. The CATIE-AD study has substantially added to our knowledge, but more information is still necessary. We make this statement based on the prevalence of the condition and uncertainty about the balance between risks and benefits in these patients. While the increased risk of death in elderly dementia patients treated with atypical antipsychotics was small, the demonstrable benefits in the RCTs were also small. Information is needed on how the risk compares to risks for other treatments.

An established framework for evaluating the relevance, generalizability, and applicability of research includes assessing the participation rate, intended target population, representativeness of the setting, and representativeness of the individuals, along with information about implementation and assessment of outcomes. As these data are reported rarely in the studies we reviewed, conclusions about applicability are necessarily weak. In many cases, enrollment criteria for these trials were highly selective (for example, requiring an open-label run-in period). Such highly selective criteria may increase the likelihood of benefit and decrease the likelihood of adverse events. At best, we judge these results to be only modestly applicable to the patients seen in typical office-based care.

With few exceptions, there is insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotic medications for any of the off-label indications, either vs. placebo or vs. active therapy.

More head-to-head trials comparing atypical antipsychotics are needed for off-label indications other than dementia.

Table A. Summary of Evidence-Efficacy of Off-Label Use of Atypical Antipsychotics

Condition	Strength of evidence	Conclusion
Behavioral problems in dementia	Moderate for risperidone, olanzapine, and quetiapine; low for aripiprazole.	• A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. • Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found 3 studies of quetiapine; they were too dissimilar in their design and outcomes to pool. • A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine, and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo. • We found no studies of ziprasidone for agitation and behavioral disorders in elderly persons with dementia.
Specific categories of depression: **a. Inadequate response to SRI** **b. With psychotic features** **c. With bipolar disorder**	Moderate that olanzapine, whether used as monotherapy or to augment therapy, does not improve outcomes at 8 weeks in SRI-resistant depression; low for all atypical antipsychotics for other depression indications, due to small studies, inconsistent findings, or lack of comparisons to usual treatments.	• For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks. • In 2 trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined as the trial lacked a fluoxetine-only comparison arm. • For bipolar depression, olanzapine and quetiapine were superior to placebo in 1 study for each drug, but data are conflicting in 2 other studies that compared atypical antipsychotics to conventional therapy. • We found no studies of aripiprazole for depression.
Obsessive-compulsive disorder	Moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.	• We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment. • A moderate amount of evidence from 9 trials shows that these drugs have a clinically important beneficial effect when used as augmentation therapy for patients who failed to adequately respond to SRI therapy. • We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.

Condition	Strength of evidence	Conclusion
Posttraumatic stress disorder	Low for risperidone for combat-related PTSD due to sparse data; very low for risperidone and olanzapine for treating non-combat-related PTSD.	• We found four risperidone and two olanzapine trials of over 6 weeks for PTSD. • There were 3 trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. • We found 3 trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy. • We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.
Personality disorders	Very low due to small effects, small size of studies, and limitations of trial quality.	• 4 RCTs, each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder. • The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small. • Olanzapine caused significant weight gain in all studies. • Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in 1 small 9-week trial. • Aripiprazole was more effective than placebo for the treatment of borderline personality in 1 small 8-week trial.
Tourette's syndrome in children/adolescents	Low for risperidone; very low for ziprasidone.	• We found 4 trials of risperidone and 1 of ziprasidone for this condition. • The little evidence available is inconclusive about the efficacy of either drug. • We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.
Autism in children/Adolescents	Low for risperidone due to sparse data.	• Just before this report was published, the FDA approved risperidone for use in autism • Two trials of 8 weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. • We found no trials of olanzapine, quetiapine, ziprasidone, or aripiprazole for autism.

Abbreviations**:** FDA = U.S. Food and Drug Administration; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SRI = serotonin reuptake inhibitor.

Table B. Summary of Adverse Event and Safety Findings Concerning Off-Label Use of Atypical Antipsychotics for Which There is Moderate or Strong Evidence

Side effect	Head-to-head trials	Active control trials	Placebo controlled trials
Mortality (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for atypical antipsychotics compared to placebo.
Cardiovascular (not including cerebrovascular accident)	Insufficient evidence of difference.	Insufficient evidence of difference.	Insufficient evidence of difference.
Cerebrovascular accident (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for risperidone and olanzapine compared to placebo.
Extrapyramidal symptoms	More common in olanzapine and risperidone than in quetiapine.	Insufficient evidence of difference.	More common in risperidone, olanzapine, aripiprazole, and ziprasidone than placebo, quetiapine insufficiently studied.
Neurological (fatigue, headaches, dizziness; excludes movement disorders)	Insufficient evidence of difference.	Insufficient evidence of difference.	More common in risperidone, olanzapine and aripiprazole than placebo; other drugs insufficiently studied.
Sedation	Insufficient evidence of difference.	More common in olanzapine than mood stabilizers.	More common in atypical antipsychotics than placebo.
Weight gain	More common in olanzapine than other atypical antipsychotics.	More common in olanzapine than conventional antipsychotics.	More common in olanzapine and risperidone than placebo; other drugs insufficiently studied.

Introduction

Background

Antipsychotic medications, widely used for the treatment of schizophrenia and other psychotic disorders, are commonly divided into two classes, reflecting two waves of historical development. The conventional antipsychotics--also called typical antipsychotics, conventional neuroleptics, or dopamine antagonists--first appeared in the 1950s and continued to evolve over subsequent decades, starting with chlorpromazine (Thorazine), and were the first successful pharmacologic treatment for primary psychotic disorders, such as schizophrenia. While they provide treatment for psychotic symptoms - for example reducing the intensity and frequency of auditory hallucinations and delusional beliefs - they also commonly produce movement abnormalities, both acutely and during chronic treatment, arising from the drugs' effects on the neurotransmitter dopamine. These side effects often require additional medications, and in some cases, necessitate antipsychotic dose reduction or discontinuation. Such motor system problems spurred the development of the second generation of antipsychotics, which have come to be known as the "atypical antipsychotics."

Currently, the U.S. Food and Drug Administration (FDA)-approved atypical antipsychotics are aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Off-label use of the atypical antipsychotics has been reported for the following conditions: dementia and severe geriatric agitation, depression, obsessive-compulsive disorder, posttraumatic stress disorder, and personality disorders. The purpose of this Evidence Report is to review the evidence supporting such off-label uses of these agents. We were also asked to study the use of the atypical antipsychotics for the management of Tourette's Syndrome and autism in children. The medications considered in this report are those listed above; however, we have excluded clozapine, which has been associated with a potentially fatal disorder of bone-marrow suppression and requires frequent blood tests for safety monitoring. Because of these restrictions, it is rarely used except for schizophrenia that has proven refractive to other treatment.

Dementia and Severe Geriatric Agitation

Dementia is a disorder of acquired deficits in more than one domain of cognitive functioning. These domains are memory, language production and understanding, naming and recognition, skilled motor activity, and planning and executive functioning. The most common dementias – Alzheimer's and vascular dementia - are distinguished by their cause. Alzheimer's dementia occurs with an insidious onset and continues on a degenerative course to death after 8 to10 years; the intervening years are marked by significant disturbances of cognitive functioning and behavior, with severe debilitation in the ability to provide self-care. Vascular dementia refers to deficits of cognitive functioning that occur following either a cerebrovascular event – a stroke – leading to a macrovascular dementia, or, alternatively, more diffusely located changes in the smaller blood vessels, leading to a microvascular dementia. These (and other) dementia types commonly co-occur. Psychotic symptoms are frequent among dementia patients and include

auditory hallucinations, believing that one's personal belongings have been stolen, or believing that unknown others are cohabiting with the patient (phantom boarders). Although the cognitive deficits can be severe, it is the behavioral disturbances (such as yelling or combativeness with caregivers) that typically interfere with independent living and necessitate placement in a nursing home.

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

Depression

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

Unipolar depression refers to the DSM disorder called major depressive disorder and is defined by episodes of at least a majority of the above symptoms lasting at least two weeks. A particularly severe form of major depressive disorder occurs when the depression is accompanied by psychotic symptoms such as auditory hallucinations. Current treatment guidelines for the pharmacologic treatment of major depression are expressed algorithmically as a flowchart, with later steps tried after the failure of the earlier steps.[1] Failure may occur for a variety of reasons, including intolerable side effects or lack of improvement after treatment of an appropriate duration. The mainstays of treatment are the antidepressants, including the serotonin reuptake inhibitors (SRIs), including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; the tricyclic antidepressants, including amitriptyline, imipramine, nortriptyline, and desipramine; and other drugs with dual reuptake inhibition or other mechanisms, including bupropion, duloxetine, mirtazapine, and venlafaxine. Other treatments used include augmenting agents, medications that are not themselves antidepressants, but that speed or improve the antidepressant activity; various psychotherapies; and electroconvulsive therapy. Because of their serotonergic effects, the atypical antipsychotics have been tested as augmenting agents. For depression with psychotic features, the recommended psychopharmacologic treatment consists of the simultaneous use of antidepressants and antipsychotics - most often atypical antipsychotics.[1, 2]

Bipolar depression refers to the depressed phase of bipolar disorder, a severe mental illness with mood fluctuations both below (depressed) and above (manic) the normal euthymic state. (It is also informally known as manic depression, although that term has been dropped from the official diagnostic terminology.) Treatment of the depressed phase is more complicated than the treatment of unipolar depression because one of the standard treatments for depression,

antidepressant medication, has been implicated in a mood destabilization phenomenon known as "switching," in which the mood of a patient with bipolar depression is not restored to euthymia but moves instead into the elevated mood state of mania. The optimal treatment of bipolar depression is not yet known, but current guidelines suggest that initial treatment with a mood stabilizing agent or contemporaneous use of a mood-stabilizing agent along with an antidepressant may lower the risk of switching. Because the atypical antipsychotics have FDA approval for use as mood stabilizing agents in the treatment of manic or mixed states, they have been used in combination with antidepressants for the treatment of bipolar depression.

Depressive symptoms may also occur during primary psychotic disorders. The DSM-IV-TR discourages the separate diagnosis of major depression during schizophrenia, although it acknowledges that such comorbidity is common. A related disorder, schizoaffective disorder, combines chronic psychotic symptoms similar to schizophrenia with more pronounced episodic mood disturbances, which can resemble either major depression or bipolar disorder. Whether the antipsychotics medications used to treat primary psychotic disorders also effectively treat comorbid depression is not well known.

Obsessive-Compulsive Disorder

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

Posttraumatic Stress Disorder

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

Personality Disorders

A Personality Disorder is "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment."[3] The current edition of the DSM defines 10 such disorders. Optimal treatment of such disorders is not well understood, although some of the disorders are the focus of active research. Because of the long-term nature of the disorders, they are often treated through psychotherapy in an attempt to facilitate long-term personality change, while psychiatric medications are thought to play a role in moderating some of the symptomatic manifestations. Only two personality disorders have been treated in clinical trials with atypical antipsychotics: schizotypal personality disorder (SPD) and borderline personality disorder (BPD).

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

BPD's essential characteristic is instability in interpersonal relationships, self-image, and mood, along with impulsive behavior, intense anger, and recurrent suicidal gestures or attempts. There are often severe dissociative symptoms and paranoid ideation, which may occur or worsen with stress. BPD is a significant cause of psychiatric morbidity, and, because of the increased risk for suicide, mortality. Effective treatment of BPD is an area of active research. The cornerstone of treatment is psychotherapy of various kinds, with dialectical behavior therapy and mentalization-based therapy, among others, having shown some efficacy in clinical trials.[4] Psychiatric medications are also commonly used, to treat both comorbid conditions, such as mood disorders, and the symptoms of BPD, although the evidence supporting such use is not strong. Because of the occurrence of psychotic symptoms, and because atypical antipsychotics have mood stabilizing properties, they are commonly tried in the treatment of BPD.

Tourette's Syndrome

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

Autism

Autism is characterized by abnormal development of social interaction and communication skills and significant restriction of activities, interests, and behaviors, with symptoms developing by age three. It is categorized as one of the pervasive developmental disorders, which also include Asperger's disorder, and the catchall category of Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS). Depending on the severity of symptoms, differentiating

autism, Asperger's disorder, and PDD NOS can be difficult, and they are occasionally grouped together for study. The primary treatment for autism is therapy for behavior modification, special education, and family counseling. Psychiatric medications are often used for symptom control; commonly used medications include antidepressants, mood stabilizers, and antipsychotics, including the atypicals.

Both Tourette's Syndrome and autism can persist into adulthood, but the evidence reviewed in this report applies only to children and adolescents.

Scope and Key Questions

The EPC was originally asked to investigate the following questions:

Key Question 1. What are the leading off-label uses of antipsychotics in the literature?

Key Question 2. What does the evidence show regarding the effectiveness of antipsychotics for off-label indications, such as depression? How do antipsychotic medications compare to other drugs for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses?

Key Question 4. What are the potential adverse effects and/or complications involved with off-label antipsychotic prescribing?

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

Representatives of the topic nominator, the state of Washington, narrowed the scope of the project to the atypical class of antipsychotics (excluding clozapine, because of its limited use in resistant schizophrenia) in December, 2004. This nominator also narrowed the psychiatric conditions to dementia/geriatric agitation, depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and personality disorders among adults and autism and Tourette's syndrome among children/adolescents.

Methods

Topic Development

The Agency for Healthcare Research and Quality (AHRQ) originally assigned this topic to us based on a nomination by the Department of Labor and Department of Corrections in the state of Washington. Later, we were asked by AHRQ to develop this as a comparative effectiveness report. Such reviews are being conducted by the Evidence-based Practice Centers (EPCs) for the AHRQ Effective Health Care program. These reviews are one aspect of the program, developed in response to Section 1013 of the Medical Modernization Act (MMA), which called for AHRQ to conduct a range of activities pertinent to evaluating, generating, and disseminating evidence about the comparative effectiveness of medications, devices, and other interventions. The evidence report focuses on the atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) as used for the following psychiatric conditions: dementia/severe geriatric agitation, depression, obsessive-compulsive disorder (OCD), personality disorders, and post-traumatic stress disorder (PTSD). We were asked to review use in children/adolescents for autism and Tourette's syndrome if time and resources permitted.

Search Strategy

Our library searches began in December, 2004, with a search of the Cochrane Database of Reviews of Effectiveness (DARE) and Pubmed. In early January, 2005, we followed with a search of PsycInfo and the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies are available in Appendix A.

AHRQ is dedicated to identifying as many studies as possible that are relevant to the questions for each of its systematic reviews. In order to do so, we supplemented the usual electronic database and hand searches of the literature by systematically requesting information (e.g., details of studies conducted) from pharmaceutical industry stakeholders. The Effective Health Care Program Scientific Resource Center at Oregon Health & Science University requested unpublished data from the five manufacturers of atypical antipsychotics.

In addition, several recent evidence reports related to our research subject were identified. In April, 2004, the EPC at McMaster University completed an evidence report on pharmacological treatment of dementia. We examined the references of the report and ordered any articles that we had not already identified. In December, 2004, the EPC at Oregon Health & Science University completed a drug class review on atypical antipsychotics. Although that report focused on FDA-approved uses (treatment of schizophrenia and bipolar disorder), it contained a chapter on behavioral and psychological symptoms of dementia. We reviewed this chapter and ordered any relevant studies that our literature search had not captured.

Technical Expert Panel

This evidence report was guided by a Technical Expert Panel (TEP). We invited a distinguished group of scientists and clinicians to participate in the TEP for this report. We aimed to have at least one expert on each psychiatric condition on our TEP. TEP conference calls were held in April and May 2005.

The TEP indicated that trials less than six weeks in length should be excluded from the efficacy analyses as six weeks is an insufficient time to assess outcomes. The TEP was instrumental in deciding appropriate outcome measures for specific psychiatric conditions and identifying recently published or ongoing clinical trials. The TEP reviewed the draft evidence report and provided critical feedback.

Study Selection

Two trained researchers reviewed the list of titles and selected articles to obtain. Each article retrieved was reviewed with a brief screening form (see Appendix B) that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Again, to be included in our evidence report, the study had to involve aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone for any of the following psychiatric conditions: dementia, severe geriatric agitation, depression, obsessive-compulsive disorder (OCD), personality disorders, posttraumatic stress disorder (PTSD), autism, or Tourette's syndrome. Only studies on humans were included. Our efficacy analyses included only controlled trials of at least 6 weeks duration. Our adverse events analyses included controlled trials of any duration and case series or cohort studies with a comparison group of more than 1,000 subjects. (We found no case control studies.) Observational studies of this size were included because they may provide evidence about the possible existence of rare adverse events that are not normally well assessed in clinical trials of more modest size.

Data Abstraction

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

For efficacy outcomes, a statistician extracted data. Efficacy outcomes abstracted are listed by condition in Table 1 below. Based on important outcomes listed by the TEP, a psychiatrist chose which outcomes were most appropriate to pool. Poolability across studies was also important; the more trials that reported an outcome measure, the more likely we were to use it in

our analysis. For each treatment or placebo arm within a trial, the sample size, mean outcome, and standard deviation were extracted. If a study did not report a follow-up mean or if a follow-up mean could not be calculated from the given data, the study was excluded from analysis. For those trials that did not report a follow-up standard deviation, we imputed one by assigning the average standard deviation from other trials that reported the standard deviation for the same outcome. If fewer than two trials were available with standard deviations, then we imputed the follow-up standard deviation by taking one-fourth the theoretical range of the scale.

Table 1. Efficacy outcomes abstracted

Conditions	Outcome Measures
Autism	Aberrant Behavior Checklist – **ABC** Childhood Autism Rating Scale
Dementia-agitation	Agitation-Calmness Evaluation Scale - **ACES** Behavioral Pathology in Alzheimer's Disease Rating Scale - **BEHAVE-AD** (subscale: aggressiveness) Cohen-Mansfield Agitation Inventory - **CMAI** Neuropsychiatric Inventory, Nursing Home - **NPI-NH** (subscale: agitation) Neuropsychiatric Inventory - **NPI** (subscale: agitation) Positive and Negative Symptom Scale - **PANSS** (subscale: excitement)
Dementia-cognition	Mini Mental Status Exam - **MMSE** Alzheimer's Disease Assessment Scale - **ADAS** (cognition scale)
Dementia-global	Neuropsychiatric Inventory, Nursing Home - **NPI-NH** (total) Neuropsychiatric Inventory - **NPI** (total) Clinician's Interview-Based Impression of Change - **CIBIC** Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale - **E-BEHAVE-AD** (total) Behavioral Pathology in Alzheimer's Disease Rating Scale - **BEHAVE-AD** (total)
Dementia-improvement	Clinical Global Impression Scale - **CGI:I** (improvement subscale)
Dementia-psychosis	Neuropsychiatric Inventory, Nursing Home - **NPI-NH** (subscale: psychosis) Positive and Negative Symptom Scale - **PANSS** (subscale: psychosis) Behavioral Pathology in Alzheimer's Disease Rating Scale **BEHAVE-AD** (sum of paranoid and delusional ideation and hallucinations items) Brief Psychiatric Rating Scale - **BPRS** (subscale: psychosis) - it is the sum of unusual thought content, paranoia(or suspiciousness), hallucinations (or hallucinatory behavior), disorganized thinking (or conceptual disorganization)
Dementia-severity	Clinical Global Impression Scale - **CGI:S** (severity subscale)
Depression	Hamilton Depression Scale - **HAM_D** (HDRS) Montgomery - Asberg Depression Rating Scale - **MADRS** Bech-Rafaelson Melancholia Scale - **BRMES** Depression cluster - **PDC** Center for Epidemiologic Studies Depression Scale - **CES-D** Brief Symptom Inventory - **BSI**
Depression-improvement	Clinical Global Impression Scale - **CGI:I** (improvement subscale)
OCD	Yale - Brown Obsessive Compulsive Scale - **YBOCS**
OCD-severity	Clinical Global Impression Scale - **CGI:S** (severity subscale)
PTSD	Clinician Administered PTSD Scale - **CAPS**
PTSD-depression	Center for Epidemiologic Studies Depression Scale - **CES-D** Hamilton Depression Scale - **HAM-D** Beck Depression Inventory - **BDI**
Tourette's Syndrome	Tic Symptom Self Report – **TSSR** Yale Global Tic Severity Scale - **YGTSS**

Adverse Events

Adverse events were recorded onto a spreadsheet that identified each trial group, the description of the adverse event from the original article, the number of subjects in each group, and the number of subjects affected. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event.

If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume an adverse event occurred unless the trial report specifically stated that some number of events were observed. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed. Taking the opposite tack, namely assuming a particular adverse event did not occur in any study if it was not mentioned, certainly underestimates the number of patients for whom a particular adverse event occurred.

After abstracting the data, we identified mutually exclusive groups of similar events, based on clinical expertise. For example, events that affected the head, ear, eye, nose, or throat were grouped together as HEENT. A group could contain subgroups; for example, decreased salivation, increased salivation, and eye irritation are subgroups of HEENT, with their own analyses. For each adverse-event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the medication groups in the relevant trials who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then report the analogous counts for the control groups in the relevant trials.

Quality Assessment

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

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

To arrive at a quantitative measure, we used the Jadad scale, which was developed for drug trials. This method measures quality on a scale that ranges from 0-5, assigning points for randomization, blinding, and accounting for withdrawals and dropouts.[5] Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared

with trials scoring 3-5.[6] The latter have been called "good" quality and the former called "poor" quality.

Applicability

Effectiveness studies compare a new drug with viable alternatives rather than with placebo; they produce health, quality of life, and economic outcomes data under real world conditions. For example, an effectiveness trial of a new asthma drug would include asthma-related emergency room visits, the frequency and costs of physician visits, patients' quality of life, patient compliance with the medications, acquisition costs of the medications, and frequency and costs of short-term and long-term adverse events.

Clinicians and policymakers often distinguish between the efficacy of an intervention (the extent to which the treatment works under ideal circumstances) and the effectiveness of the intervention (the extent to which the treatment works on average patients in average settings). Efficacy studies tend to be smaller, to be performed on referred patients and in specialty settings, and to exclude patients with comorbidities. Effectiveness studies are larger and more generalizable to practice. Please be aware that the vast majority of studies included in our report are efficacy studies. However, effectiveness studies are included in our analyses of adverse events.

Rating the Body of Evidence

We assessed the overall quality of evidence for outcomes using a method developed by the Grade Working Group, which classified the grade of evidence across outcomes according to the following criteria:[7]

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

GRADE also suggests using the following scheme for assigning the "grade" or strength of evidence:

Criteria for assigning grade of evidence
Type of evidence Randomised trial = high Observational study = low Any other evidence = very low **Decrease grade if**: • Serious (-1) or very serious (-2) limitation to study quality • Important inconsistency (-1) • Some (-1) or major (-2) uncertainty about directness • Imprecise or sparse data (-1) • High probability of reporting bias (-1) **Increase grade if**: • Strong evidence of association-significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association-significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)

For this report, we used both this explicit scoring scheme and the global implicit judgment about "confidence" in the result. Where the two disagreed, we went with the lower of the two classifications.

Data Synthesis

We constructed evidence tables displaying the study characteristics and results for all included studies (Appendix C). Trials that evaluated one atypical antipsychotic against another and provided direct evidence of comparative effectiveness are classified as "head-to-head" trials. "Active" controlled trials compare an atypical antipsychotic with another class of medication. Trials that compare atypical antipsychotics with a placebo are referred to as "Placebo" controlled trials. Finally, trials that compare an antipsychotic taken with another medication with the other medication alone were examined (referred to as augmentation trials). We provide four separate evidence tables, one for each type of study (head-to-head, active control, placebo control, and augmentation). We also include an evidence table of large case series and cohort studies identified for our adverse events analyses.

Our *a priori* analytic plan was to summarize the evidence for efficacy (versus placebo or versus conventional therapy) within condition (dementia, depression, personality disorders, etc.) and across class (all five atypical antipsychotics); the evidence of risks (adverse events) was summarized within drug (each atypical antipsychotic separately) across condition. This strategy has ample support in the literature, with many examples of drugs that demonstrate similar efficacy across a class of drugs and are then distinguished on the basis of their adverse events profile.

Because the topic nominator of this report was interested primarily in efficacy, our synthesis deals both with efficacy (do these drugs work?) and comparative effectiveness (are there differences between drugs?).

Efficacy and Comparative Effectiveness

For the efficacy and comparative effectiveness analyses, we focused on controlled trials that reported outcomes with at least 6 weeks follow-up. Effect sizes were calculated for each comparison. If all trials within a condition and subgroup used the same scale, then the effect size did not need to be standardized and a mean difference was calculated. For subgroups where pooling was done across several scales, we calculated an unbiased estimate using the Hedges' g effect size.[8] Since most of the scales used as outcome measures in the pooled analyses are scored so that more severely symptomatic persons have higher scores, a negative effect size indicates that the atypical drug has a higher efficacy than does the comparison arm (active control or placebo arm). However, for OCD, our approach was to calculate a risk ratio for each trial based on the number of "responders" within the treatment and placebo arms, because the primary outcomes were reported this way in the original trials.

For trials that were judged sufficiently clinically similar to warrant meta-analysis, we estimated a pooled random-effects estimate[9] of the overall mean difference in outcome measure. The individual trial mean differences are weighted by both within-study variation and between-study variation in this synthesis. We pooled the risk ratios using the same method as above for the OCD condition. We constructed forest plots in which each individual trial mean difference is shown as a box whose area is inversely proportional to the estimated variance of the mean difference in that trial. The trial's confidence interval is shown as a horizontal line through the box. The pooled "weighted mean difference" and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate value. A vertical solid line at zero indicates no effect of medication. We also report the chi-squared test of heterogeneity p-value based on Cochran's Q[8] and the I-squared statistic.[10] A significant Q statistic or I^2 values close to 100 percent represent very high degrees of heterogeneity. I^2 values of 25 percent, 50 percent, and 75 percent represent low, moderate, and high heterogeneity. The numbers of trials of atypical antipsychotics for depression, dementia, and OCD were sufficient for meta-analysis. For the pooled analysis of trials of OCD, the calculations were performed on the relative risk of "responding" to the drug, so the "no effect" line is at a relative risk of 1. We also calculated Number Needed to treat (NNT) where applicable.

We assessed publication bias for each condition that was pooled. Tests were conducted using the Begg[11] adjusted rank correlation test and the Egger[12] regression asymmetry test.

All meta-analyses were conducted with Stata statistical software, version 8.2 (Stata Corp., College Station, Texas).

For groups of trials not judged sufficiently clinically similar to support meta-analysis, we performed a narrative synthesis. Trials of atypical antipsychotic drugs for PTSD, personality disorders, Tourette's syndrome, and autism were summarized narratively.

Adverse Events

For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings

of other systematic reviews and meta-analyses that treated these drugs as a class. For our own analyses, we divided the study populations into three groups to make them more clinically homogeneous with respect to adverse events: dementia (elderly subjects), autism and Tourette's (children and adolescents), and everything else (adults).

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

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

Peer Review

We requested review of the draft report from our Technical Expert Panel and various additional content and methods experts. In addition, review was performed by the Effective Health Care Program Scientific Resource Center (SRC) located at Oregon Health & Science University and by pharmaceutical companies. More than 100 articles, abstracts, and reports were submitted by these reviewers for consideration. A blinded list of peer reviewer comments and author responses has been provided to the SRC.

Results

Literature Flow

In total, RAND reviewers examined 2,782 titles for the draft version of this report. The electronic literature search identified 2,265 titles (Figure 1). An additional eight articles were suggested from the personal libraries of the project members. Four additional articles were suggested by our TEP members. Reference mining identified another 396 potentially relevant titles. We received scientific information packets from all five drug manufacturers; these identified an additional 109 potentially relevant titles. After review of the draft report, pharmaceutical companies submitted an additional 84 conference presentations, articles, and unpublished reports.

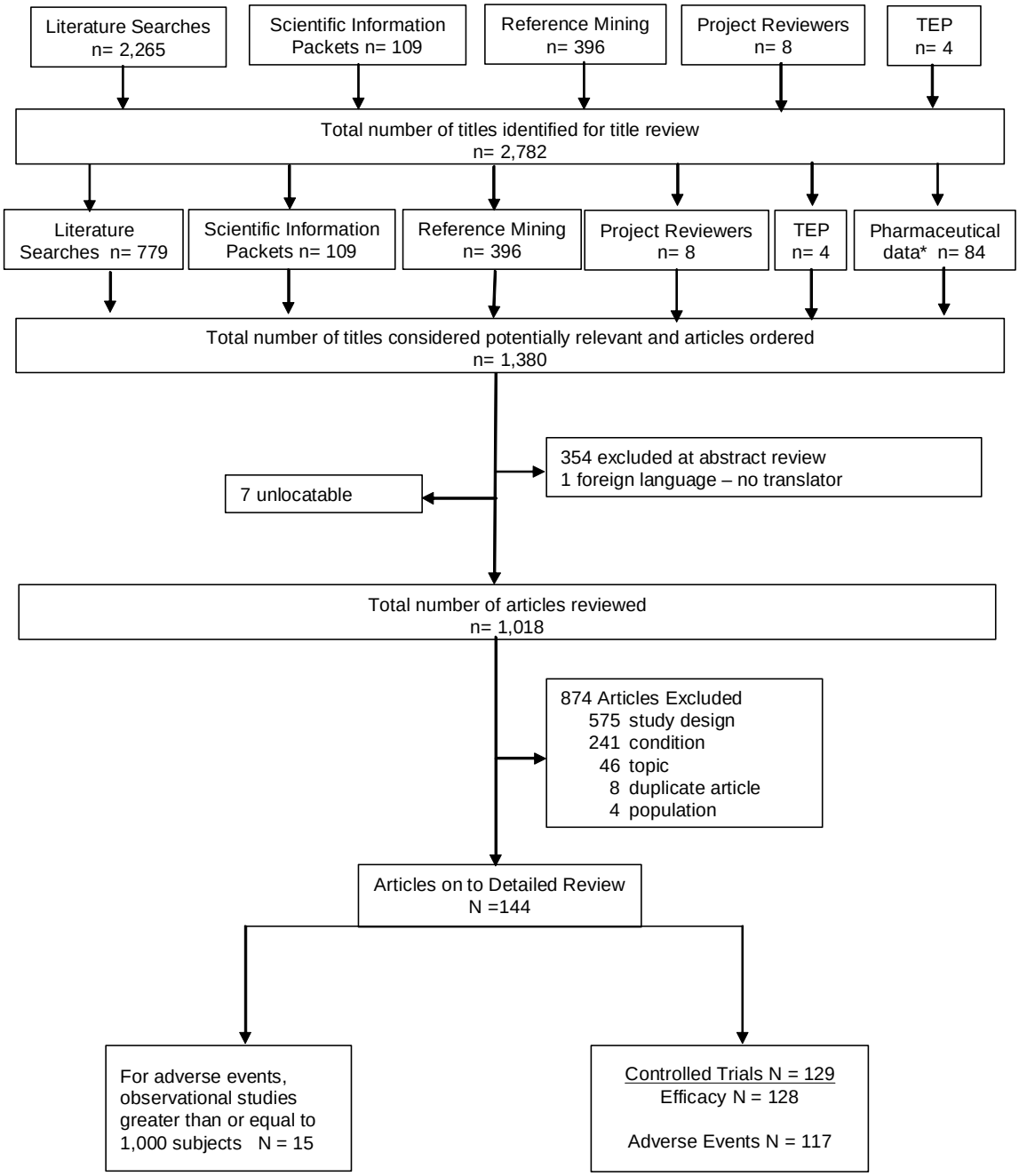
Of the titles identified through our electronic literature search, 1,486 were rejected as not relevant to our project, leaving 1,380 total from all sources. Repeat review by the research team excluded an additional 354 titles. One article, published in a foreign language was excluded due to lack of translation resources. Seven titles could not be located even after contracting with Infotrieve, a private service that specializes in locating obscure and foreign scientific publications.

Screening of retrieved articles/reports resulted in exclusion of 874: 575 due to study design; 241 had no psychiatric condition of interest; 46 did not discuss a drug (topic) of interest; eight duplicate articles- accidentally ordered; and four for population. The remaining 129 articles reporting on randomized controlled trials were reviewed in detail for efficacy and safety results. Fifteen large cases series and cohort studies were also reviewed for the safety analysis. (For a list of excluded studies, please refer to Appendix D).

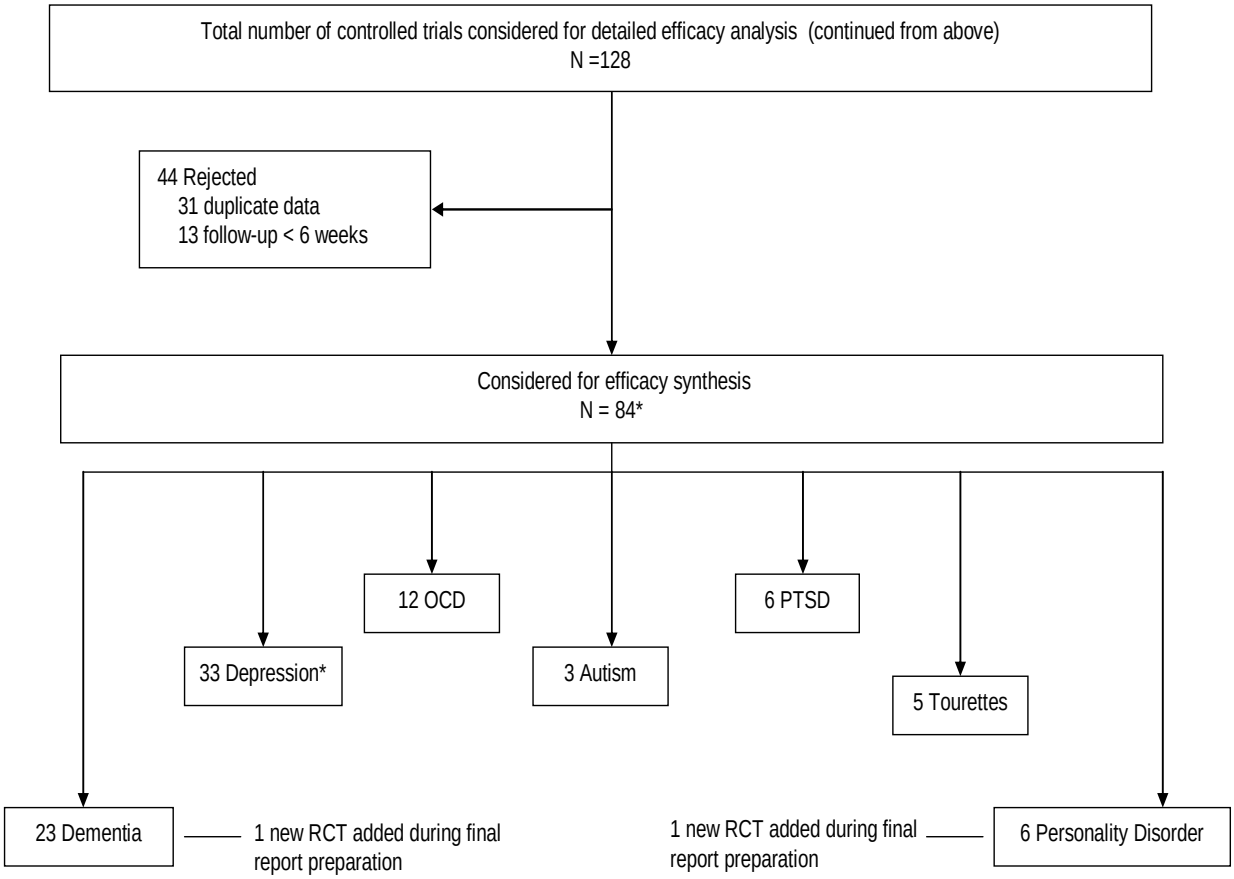
The second page of Figure 1 displays the breakdown of the 128 randomized controlled trials that reported efficacy results. Thirty-one were rejected because they represented multiple reports of many studies. We also rejected 13 reports of trials less than 6 weeks in length, per our Technical Expert Panel. The remaining 84 randomized clinical trials were reviewed for our efficacy synthesis, several of which included patients with multiple conditions. For dementia, we used a high-quality recently published meta-analyses rather than conducting our own.

As the report was being prepared for distribution, there were two RCTs newly published. One study was an assessment of aripiprazole for patients with personality disorders and the other was the Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Diesease (CATIE-AD) trial.

Figure 1. Literature Flow



*submitted after review of draft report



*conditions not mutually exclusive

Key Question #1: What are the leading off-label uses of antipsychotics in the literature?

Key Point

The most common off-label uses of atypical antipsychotics we found in the literature were the treatment of agitation in dementia, depression, obsessive-compulsive disorder, PTSD, personality disorders, Tourette's syndrome, and autism. In October 2006, risperidone was approved for use in autism.

Key Question #2: What does the evidence show regarding the effectiveness of antipsychotics for off-label indications, such as depression? How do antipsychotic medications compare with other drugs for treating off-label indications?

Dementia

Key Points

- A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes.
- Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found 3 studies of quetiapine; they were too clinically dissimilar to pool.
- A large head-to-head placebo controlled trial concluded there were no differences in time-to-discontinuation of medication between risperidone, olanzapine, quetiapine and placebo. Efficacy outcomes favored risperidone and olanzapine and tolerability outcomes favored quetiapine and placebo.
- We found no studies of ziprasidone for this indication.

Schneider and colleagues recently published a meta-analysis on the efficacy and safety of atypical antipsychotics for dementia.[13] These same authors published an earlier meta-analysis of the risk of death with atypical antipsychotic treatment for dementia.[14] The new meta-analysis included only randomized, placebo controlled, double-blind parallel group trials with patients with Alzheimer's disease or dementia that assessed atypical antipsychotics marketed in the United States. This group included three trials of aripiprazole, five trials of olanzapine, three trials of quetiapine, and four trials of risperidone. The authors employed a comprehensive search for published and unpublished data, including obtaining data from abstracts presented at

meetings and from the trials' sponsors. Five trial reports were obtained via a Medline search, and 13 posters and slide presentations from medical conferences yielded an additional 10 trials. In total, the authors identified 18 placebo-controlled trials, but for three trials of risperidone, data were insufficient to be included in the meta-analysis. Of the 15 included trials, 11 were conducted in nursing home patients. The duration of trials ranged from 6 to 26 weeks, with 10 of the 15 trials being 10 or 12 weeks in duration. In total, 3,353 patients were randomized to drug and 1,757 to placebo. Overall, 87 percent of subjects were diagnosed with Alzheimer's disease. The weighted mean age was 81.2 years, and 70 percent of subjects were female. The extent of cognitive impairment ranged from mild to severe.

The authors conducted meta-analyses of separate outcomes for each drug. A summary of results is presented in Table 2. On a variety of continuous and dichotomous outcomes, including the Brief Psychiatric Rating Scale (BPRS), the NeuroPsychiatric Inventory (NPI), and the Cowen-Mansfield Agitation Inventory (CMAI), and on improvement as assessed by greater than 50 percent improvement in the total NPI score or NPI psychosis subscale, the pooled results yielded small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects on continuous outcomes that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Data were insufficient to pool dichotomous outcomes for studies of olanzapine. The three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.

In the trials of risperidone, four pooled studies yielded a statistically significant effect in the Behavior Pathology and Alzheimer's Disease rating scale (Behave AD), and three pooled studies yielded a statistically significant result on the CMAI total score. With responders defined as those with greater than 50 percent improvement in Behave AD total score, three studies yielded a statistically significant odds ratio of 1.79.

In a subgroup analysis, the authors assessed the effect of atypical antipsychotics on psychosis subscales of various outcomes. In general, with the exception of three trials of risperidone assessed using the Behave AD psychosis subscale, no statistically significant results were found.

Table 2. Pooled results of placebo-controlled trials of atypical antipsychotics for patients with dementia and behavioral disturbances or agitation

Drug, number of trials	Outcome measure	Pooled Result Weighted mean difference
Aripiprazole, 3 trials	BPRS total NPI total	-2.49 (-4.05,-0.94) -3.63 (-6.57, -0.69)
Aripiprazole, 2 trials	CMAI total	-4.05 (-6.58, -1.52)
Olanzapine, 3 trials	BPRS total NPI total	-0.92 (-2.48, 0.63) -1.74 (-4.68, 1.20)
Risperidone, 4 trials	BEHAVE-AD total	-1.48 (-2.35, -0.61)
Risperidone, 3 trials	CMAI total	-3.00 (-4.22, -1.78)

Drug, number of trials	Outcome measure	Fixed effects odds ratio	NNT
Aripiprazole, 3 trials	>50% Improvement in NPI total >50% Improvement in NPI psych	1.50 (1.14, 1.99) 1.38 (1.04, 1.83)	10 (6, 27) 14 (7, 156)
Risperidone, 3 trials	>50% Improvement BEHAVE-AD total	1.79 (1.37, 2.33)	7 (5, 13)
Risperidone, 2 trials	Much/Very Much Improved CGI-C	2.01 (1.49, 2.72)	6 (4, 10)

In other subgroup analyses that combined results across drugs, there were larger effect sizes in patients without psychosis than those with psychotic symptoms. In additional subgroup analyses, the effect size for nursing home patients was almost 10 times the effect size for community living patients (0.19 and 0.02, respectively). Also, larger effects were found in the trials of patients with a lower mean Mini Mental Status Exam (MMSE) score than in the trials with patients with a higher mean score (almost three times the effect size). Interestingly, a pooled analysis of 14 trials, across drugs, yielded an effect size of a composite outcome of -0.16 (95 percent CI, -0.08, -0.24). There was marked heterogeneity, so pooled results must be interpreted with caution.

The authors note that all of the significant improvements were small, usually less than a quarter of a standard deviation. They also note that the clinical significance of these effect sizes is uncertain, as there is debate among clinicians about the importance. A limitation of the data is the drop-out rates: approximately one-third across all trials. The authors note that these efficacy data need to be balanced against the possibility of adverse effects, including death. Information on these effects is provided in our adverse events section. They conclude that "antipsychotics are modestly effective when used judiciously and there are no demonstrated, effective pharmacological alternatives."

In addition to the meta-analysis of placebo-controlled trials, we found four head-to-head comparisons of risperidone and olanzapine.[15-18] Two of the studies reported no substantive differences in efficacy between drugs among elderly patients with dementia and behavioral disturbances in 494 patients[16] and in 20 patients.[15] Differences were reported in the types of adverse effects reported, to be discussed in more detail in that section of this report. One study, reported in abstract form only,[17] assessed 29 patients with Alzheimer's dementia who were randomized to olanzapine, risperidone, or placebo, for 6 weeks. This study reported that olanzapine patients had greater improvements on certain outcome measures of tension, agitation, and resistiveness, but the results are presented in insufficient detail to draw conclusions. The last study in this group compared blood assays of anticholinergic activity in 86 patients with dementia and psychosis, randomized to olanzapine or risperidone treatment, but found no statistically significant differences between treatment groups.[18]

A recent large RCT was published that directly compared the atypical antipsychotics risperidone, olanzapine, and quetiapine to each other and to placebo.[19] The Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease (CATIE-AD) study randomized 421 outpatients with DSM-IV criteria for Alzheimer's type dementia or probable Alzheimer's Disease to risperidone (average dose 1.0 mg/day), olanzapine (average dose 5.5 mg/day), quetiapine (average dose 56.5 mg/day) or placebo. The CATIE-AD trial was designed as a "pragmatic" trial to mimic real world use, and the primary endpoint was discontinuation of the drug for either lack of efficacy or troublesome side effects. Patients enrolled had a mean age

of 78 years, were 56 percent female, 79 percent white, and 73 percent of participants lived in their own home. The mean Mini-Mental Status Exam score was 15. There were no statistically significant differences between groups in the time to discontinuation of the drug (ranging from 5.3 to 8.1 weeks). More patients discontinued quetiapine or placebo than olanzapine or risperidone due to lack of efficacy, and more patients discontinued olanzapine, risperidone, or quetiapine than placebo due to troublesome side effects. At 12 weeks, efficacy measured by the Clinical Global Impression of Change did not vary between groups, but the secondary outcomes of the Neuropsychiatric Inventory and the Brief Psychiatric Rating Scale showed greater improvements in the active-treated patients than in the placebo-treated patients (but statistical tests of differences between groups were not reported). Sedation was much more common in active-treated patients than placebo. Risperidone and olanzapine were associated with much more extrapyramidal signs or Parkinsonism than placebo or quetiapine, as were confusion and mental status changes. Although not reaching conventional statistical significance, the proportion of patients gaining more than 7 percent or body weight was twice as high in risperidone and olanzapine treated patients compared to those treated with quetiapine or placebo. Cerebrovascular accidents and deaths were uncommon in all groups.

We also found five additional active-controlled trials for dementia. Three trials compared risperidone with the conventional antipsychotic haloperidol.[20-22] One of these studies[22] was a cross-over trial. Sample sizes were 58, 120, and 344 subjects. In general, there were few reported differences in efficacy between groups in these trials. Two other trials assessed the effect of adding an atypical antipsychotic to treatment with rivastigmine.[23, 24] One of these trials assessed risperidone[23] and the other assessed quetiapine.[24] Both trials were relatively small, enrolling 65 and 80 patients, respectively. The trial of risperidone did not find any substantial benefit of adding this drug to rivastigmine, but did conclude there was no evidence of increased adverse events with their co-administration. The study of quetiapine found that neither this drug nor rivastigmine were effective in the treatment of agitation in people with dementia in institutional care. Furthermore, this paper reported that treatment with quetiapine was associated with a significantly greater cognitive decline than was treatment with placebo at 26 weeks, as assessed by the severe impairment battery.

Summary

In summary, a moderate amount of evidence from a prior meta-analysis and a new head-to-head and placebo-controlled trial suggests that the atypical antipsychotics risperidone, olanzapine, quetiapine and aripiprazole have small but significant benefits in improving a variety of symptoms in patients with dementia who have agitation or behavioral disturbances. The clinical benefits of these drugs are counterbalanced by troublesome side effects prompting discontinuation. The balance between benefits and harms is about equivalent in a population of patients, but may be distinctly tilted in one direction or the other in individuals. We found no studies of ziprasidone for this indication.

There is insufficient evidence to conclude that atypical antipsychotics are any more effective than conventional antipsychotics at controlling agitation and psychosis in dementia patients. There is evidence that adding the atypical antipsychotic quetiapine to rivastigmine produces no additional benefit. There is no consistent evidence that there are any appreciable differences in efficacy between risperidone, olanzapine and quetiapine. The overall strength of evidence for risperidone, olanzapine and quetiapine and outcomes is considered moderate, based on

heterogeneity, and that future research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. The overall strength of evidence for aripiprazole is considered low, due to sparseness of data and heterogeneity.

Depression

Key Points

- For serotonin reuptake inhibitor (SRI) resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone, at 8 weeks.

- We found only two trials of atypical antipsychotics as primary therapy for major depressive disorder with psychotic features. Olanzapine and olanzapine plus fluoxentine were compared with placebo for 8 weeks in both trials. The combination group had significantly better outcomes in the first trial; in the second trial, there were no differences between groups.

- Evidence is sparse and conflicting regarding atypical antipsychotics as primary therapy for bipolar depression, compared with conventional therapy.

- We found no studies of aripiprazole for depression.

Our literature search identified 60 reports of RCTs where an outcome measure was depression.[16, 25-83] We rejected six of these studies because treatment duration was less than 6 weeks.[48-53] Many of the remaining trials assessed conditions outside the scope of this report, such as schizophrenia or schizoaffective disorder, or included mixed populations where the majority of patients had schizophrenia or schizoaffective disorder, and depression was often a secondary outcome.[25, 29, 31, 34, 35, 39, 41, 46, 54-64] Other studies reporting depression outcomes included bipolar disorder and acute mania;[32, 65] maintenance of remission in bipolar disorder;[37, 38, 40, 66, 67] trials with obsessive-compulsive disorder patients;[68-71] trials of PTSD patients;[45, 72, 73] and trials of dementia patients.[16, 74] One study of atypical antipsychotics for generalized anxiety disorder reported depression outcomes.[33] These studies are also beyond the scope of this report. We focused our synthesis on trials of atypical antipsychotics in three conditions: as augmentation therapy for patients with treatment-resistant depression; for the primary treatment of patients with major depression with psychotic features; and as primary for patients with bipolar disorder who are experiencing a phase of depression.

Augmentation therapy in patients with treatment-resistant depression

We identified nine reports of the use of an atypical antipsychotic as augmentation therapy for patients with treatment-resistant depression.[30, 43, 44, 47, 75-79] Two reports were of the same study, one in abstract form[75] and the other as a peer-reviewed journal article;[47] and one abstract was a subgroup analysis of a trial presented in another abstract, leaving seven unique trials. Four reports were in peer-reviewed journals,[30, 47, 76, 77] but three trial outcomes were published as abstracts only.[78,43, 44, 79] The salient features of these studies are presented in Table 3.

Table 3. Trials of atypical antipsychotics as augmentation therapy for major depression

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Shelton, 2001 [47]	DSM-IV criteria for recurrent major depression without psychotic features, resistant to conventional antidepressant therapy; HAM-D score of > 20; and non-response in a 6-week lead-in phase with fluoxetine	28	Olanzapine (mean dose = 12.5 mg/day) Fluoxetine (mean dose = 52 mg/day) Olanzapine (mean dose = 13.5 mg/day) + fluoxetine (mean dose = 52 mg/day) Placebo	8 weeks	Olanzapine and fluoxetine resulted in significantly greater improvements on the HAM-D scale than olanzapine alone, but were not significantly better than fluoxetine alone. Combination therapy was also significantly better than either monotherapy in improvements on the MADRS.
Shelton, 2005 [76]	DSM-IV criteria for unipolar, non-psychotic major depressive disorder and at least 1 past treatment failure with an SRI with at least 4 weeks of therapy at a therapeutic dose; and non-response to a 7-week lead-in phase with nortriptyline.	500	Olanzapine (mean dose = 8.3 mg/day) Olanzapine (mean dose = 8.5 mg/day) + fluoxetine (mean dose = 35.6 mg/day) Fluoxetine (mean dose = 35.8 mg/day) Nortriptyline (mean dose = 103.5 mg/day)	8 weeks	No significant differences among groups at 8 weeks in MADRS. Significantly greater improvements for combination therapy at weeks 2-4.
Corya, 2005 [77]	DSM-IV criteria for major depressive disorder, single episode or recurrent, without psychotic features; with a CGI-severity score of 4 or greater; documented history of failure to achieve satisfactory response to at least 6 weeks of SRI therapy at therapeutic doses; and non-response to a 7-week lead-in phase with venlafaxine	483	Olanzapine + Fluoxetine in several different doses Olanzapine (mean dose = 7.9 mg/day) Fluoxetine (mean dose = 37.5 mg/day) Venlafaxine (mean dose =275.4 mg/day)	12 weeks	No significant difference between combination therapy and any other group except olanzapine alone in MADRS at 12 weeks. Significantly greater improvements for combination therapy at weeks 2-6.

HAM-D = Hamilton Depression Scale
HAM-A = Hamilton Anxiety Scale
MADRS = Montgomery – Asberg Depression Rating Scale

Table 3. Trials of atypical antipsychotics as augmentation therapy for major depression

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Yargic, 2004 [30]	DSM-IV criteria for major depression and HAM-D scores or HAM-A scores indicating depression and anxiety	112	Paroxetine (mean dose = 28 mg/day) Paroxetine (mean dose = 27mg/day) + Quetiapine (mean dose "about" 60 mg/day at the end of the study).	8 weeks	No difference between groups in mean HAM-D or HAM-A score at week 8, but a suggestion that improvement was faster in patients treated with combination therapy.
Levitt, 2004 [44]	"unipolar non-psychotic major depression" and failed an adequate trial of an SRI or venlafaxine	43	Risperidone added to antidepressant Olanzapine added to antidepressant	6 weeks	No difference between groups for HAM-D.
Dunner, 2003 [78]	Major depression without psychotic features and a history of non-response to an adequate trial of at least 4 weeks of antidepressant therapy; a minimum MADRS score of 20; and non-response to a run-in period with sertraline	64	Sertraline (100-200 mg/day) Sertraline (100-200 mg/day) + Ziprasidone (80 mg/day) Sertraline (100-200 mg/day) + Ziprasidone (160 mg/day)	8 weeks	Comparisons across groups were not presented, but when stratified by a history of non-response (SRI or non-SRI), only those patients who had a prior history of non-SRI treatment resistance showed an improvement in MADRS score at 8 weeks.
Gharabawi, 2004 [43]	DSM-IV diagnosis of major depressive disorder, single or recurrent episode; 98% did not have psychotic features; failure to respond to other antidepressants given at adequate doses for at least 6 weeks; with non-response in a 4-6 week lead-in phase with citalopram	386	Citalopram Citalopram + risperidone (flexible dose)	24 weeks	No data on initial response to therapy; suggestion of a benefit in terms of time to relapse (102 days v. 85 days).

HAM-D = Hamilton Depression Scale
HAM-A = Hamilton Anxiety Scale
MADRS = Montgomery – Asberg Depression Rating Scale

Three trials assessed the effect of the combination of olanzapine and fluoxetine (augmentation of fluoxetine with olanzapine),[47, 76, 77] one trial each assessed the effect of augmentation of various SRIs with risperidone,[43, 79] ziprasidone,[78] and quetiapine,[30] and one study assessed adding risperidone or olanzapine to antidepressant therapy.[44] The olanzapine studies also assessed its efficacy as monotherapy. The duration of trials was from 8 to 24 weeks. The quality of most trials was fair, with only three of seven scoring 3 or greater on the Jadad scale. All trials studied patients with DSM-IV criteria for major depressive disorder, and patients with psychotic features were either excluded or constituted only a tiny fraction of enrolled patients. Some trials also required enrolled patients to exceed a certain threshold for depressive symptoms, as listed in Table 3. Almost all trials had a lead-in phase of several weeks during which patients received an antidepressant (when specified, either an SRI or venlafaxine), and only patients with an inadequate response were subsequently randomized to receive atypical antipsychotic therapy or placebo.

Most trials measured response in terms of a standardized instrument, such as the Hamilton Depression Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). In general, these trials found that olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Also, the combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine. One trial presented as an abstract assessed 386 patients with depression who were nonresponders to 4-6 weeks of therapy with citalopram.[43, 79] These patients were randomized to receive augmentation therapy with either placebo or risperidone (mean modal dose of 1.2 mg/day) for 4-6 weeks followed by a maintenance phase of 24 weeks. The study did not report differences between groups in achieving a response to therapy, but did report that patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 days v. 85 days). The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.[44]

Major depression with psychotic features

We identified two reports in which atypical antipsychotic therapy was used in patients with depression and psychosis.[26, 80] Both described the same study, one in abstract form[80] and the other as a peer reviewed publication.[26] Olanzapine and the combination of olanzapine plus fluoxetine were compared to placebo in two different 8-week trials, including 124 and 125 patients respectively, who were hospitalized for major depression with psychotic features.[26, 80] The numbers of men and women were nearly equal; average age was 41 years. The combination of fluoxetine and olanzapine produced significantly greater improvement than placebo or olanzapine alone in the HAMD-24 total score at 8 weeks in the first trial,[26] and when classified as dichotomously as "responders," or "non responders" a similar result was seen. The second trial found no differences between groups.

Bipolar depression

We identified seven reports of trials where atypical antipsychotics were used in patients with depression and bipolar disorder.[27, 28, 36, 42, 81-83] One trial was reported as both an abstract[81] and a peer-reviewed journal article.[28] Another peer-reviewed paper was a subgroup analysis of this

same trial.[27] One additional trial was published in a peer-reviewed journal,[36] and the remaining three trials were reported in abstract form only.[42, 82, 83] Two of these abstracts reported on the same trial.[82,83] Thus, there were four unique trials.

One trial[27] compared an 8-week course of placebo, olanzapine alone, or the combination of olanzapine and fluoxetine in 833 patients with DSM-IV criteria for bipolar depression (and at least one prior manic or mixed episode) and a MADRS score of at least 20.[28, 81] A second trial assessed the effect of a 12-week course of risperidone, paroxetine, or the combination when added to a mood stabilizer in 30 patients with bipolar depression, a HAM-D score of at least 18, and a score on the Young Mania Rating Scale of 8 or below.[36] A third trial, presented only in abstract form, assessed the effects of an 8-week course of quetiapine compared to placebo in 542 patients with DSM-IV criteria for bipolar depression who had a HAM-D score of 20 or greater and a Young Mania Rating Scale score of 12 or less.[42] The fourth trial, also available only in abstract form, reported the results of acute[83] and long-term treatment[82] of 410 patients with bipolar depression, a MADRS score of 20 or greater, a Clinical Global Impression severity score of four or greater, and a Young Mania Rating Score of less than 15. Treatment was either combination therapy with olanzapine and fluoxetine or lamotrigine. In general, these trials showed that olanzapine and quetiapine are more effective than placebo for treating bipolar depression but found no evidence that risperidone is more effective than paroxetine. In the study that was presented in two abstracts, the combination of olanzapine and fluoxetine had small but significant advantages over lamotrigine in several outcome measures, including the Clinical Global Impression – severity scale, the MADRS total score, and the Young Mania Rating Scale. However, there was no significant benefit in other outcome measures (proportion of patients with a 50 percent reduction in MADRS or reaching certain thresholds).

Summary

In patients with major depression who are resistant to SRI antidepressants, there is a modest amount of evidence that the addition of an atypical antipsychotic to an SRI is no more effective at 8 or 12 weeks than an SRI alone. Three trials support the finding that initial improvement (at 2-4 weeks) may be better with combination therapy. The data are sparse and conflicting about the efficacy of atypical antipsychotics for patients with major depression with psychotic features compared to conventional therapy. Sparse data support the superiority of olanzapine and quetiapine compared with placebo in treating bipolar depression, but data are conflicting regarding efficacy compared with conventional therapy. The only head-to-head study that compared olanzapine with risperidone as augmentation therapy for SRI-resistant major depression reported no differences. The overall quality of evidence for all depression outcomes and conditions is low, based on sparse data, heterogeneity, and that future research is likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

Obsessive-Compulsive Disorder

Key Points

- We found several studies of risperidone, olanzapine, and quetiapine for this indication.
- Evidence from nine trials supports the finding that these three drugs have a clinically important beneficial effect when used as augmentation therapy for patients who fail to adequately respond to SRI therapy.
- The evidence of benefit is stronger for risperidone and quetiapine than for olanzapine.
- We found no studies of ziprasidone or aripiprazole.

Our literature search identified 12 trials of atypical antipsychotics for OCD.[68, 69, 71, 84-92] Of these, six trials assessed risperidone[68, 84-88] two trials assessed olanzapine,[89, 92] and four trials assessed quetiapine.[69, 71, 90, 91] All RCTs assessed the use of an atypical antipsychotic medication as augmentation therapy for patients with OCD who were resistant to standard treatment, usually an SRI (except one study[85] discussed below). All RCTs were placebo-controlled, with parallel groups, except one trial[68] that used a complicated crossover design and involved treatment with risperidone for only two weeks. This trial was excluded from further analysis.

Trials varied in duration from 6 to 16 weeks of therapy. All but one measured a change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) as the primary outcome, with "responders" classified as those achieving 25-35 percent improvement on the Y-BOCS scale. In some cases, "responders" were also defined in terms of change in the Clinical Global Improvement (CGI) score. The size of these trials was generally small. The sample sizes ranged from 16 to 44. Quality was measured on the Jadad scale and ranged from 1-4, with nine of the 11 included RCTs scoring 3 or greater.

Nine RCTs were sufficiently clinically similar to justify meta-analysis.[69, 71, 84, 86, 87, 89-92]

The salient features of these RCTs are presented in Table 4. These nine trials were pooled on the outcome "responders," defined above, measured at 6-16 weeks of therapy (Figure 2). The random effects pooled estimate was an improvement in the relative risk of "responding" of 2.66 (95 percent CI 1.75 - 4.03). This means the number need to treat is 3.6 (2.6, 5.7). The overall score for heterogeneity was significant (p=0.036), and the I^2 statistic was 51.6 percent. Only quetiapine and risperidone were included in a sufficient number of studies to permit calculation of pooled estimates for individual drugs, and in both cases, the pooled estimate yielded a statistically significant effect favoring treatment. Relative risk of "responding" was 2.74 (95 percent CI 1.50 – 5.01) for quetiapine and 5.45 (95 percent CI 1.73 – 17.20) for risperidone. The numbers needed to treat are 3.1 (2.0, 6.5) and 2.0 (0.3, 3.3) respectively. Consequently, the evidence of benefit is stronger for quetiapine and risperidone than for olanzapine.

As eight of the nine trials included in the meta-analysis had a Jadad score of 3 or greater, a sensitivity analysis of only the "high quality" trials yielded a result nearly identical to the main result. The Begg's test was not significant (p=0.276), but the Eggar's test was significant (p=0.02), indicating the presence of unexplained heterogeneity, one explanation for which could be publication bias. However, in some situations, the Eggar's test is considered to be overly sensitive.[93] The grade of evidence for this outcome is considered moderate because of

heterogeneity, and further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Two RCTs of atypical antipsychotics could not be included in our pooled analyses.[85, 88] The first study, presented only in abstract form,[88] assessed the effect of risperidone in 16 patients with SRI-resistant OCD using the CGI score and metabolic changes in the brain as measured by positron emission tomography. Risperidone use was associated with "significant increases" in relative metabolic rate in the striatum, cingulate gyrus, and prefrontal cortex. Four of nine risperidone-treated patients and zero of six placebo-treated patients showed "clinical improvement," defined as a CGI score of 1 or 2 after 8 weeks of therapy. The second study[85] reported that augmentation therapy with risperidone was more likely to be successful in OCD patients with "bad" scores on the Iowa Gambling Task than in OCD patients with "good" scores. Not all patients in this study were resistant to SRI therapy.

A review article on the use of antipsychotic treatment for OCD was published after we concluded our analysis.[94] This narrative review included eight trials of atypical antipsychotics, which we included in our review, and concluded that the data are promising and support the use of atypical antipsychotics "such as risperidone and quetiapine as a first-line strategy for augmentation in resistant OCD." Additionally, three meta-analyses have recently been published. The first assessed double blind RCTs, identified nearly the same studies and reached similar conclusions.[95]. They concluded that there was strong evidence for both risperidone and haloperidol (a medication outside the scope of our review), and efficacy for olanzapine and quetiapine was not proven. The second meta-analysis included RCTs of antipsychotic drugs as augmentation therapy for serotonergic-resistant obsessive compulsive disorder.[96] The author identified the same 9 RCTs of atypical antipsychotics that we did, plus one additional RCT of augmentation with haloperidol. The authors reported a pooled estimate of responding of 3.31 (95 percent CI 1.40 – 7.84) for augmentation treatment with an antipsychotic. The third meta-analysis concerned just three RCTs of quetiapine augmentation, a subset of the studies used in the other meta-analyses. The study reported a statistically significant benefit for treatment with quetiapine.[97]

Summary

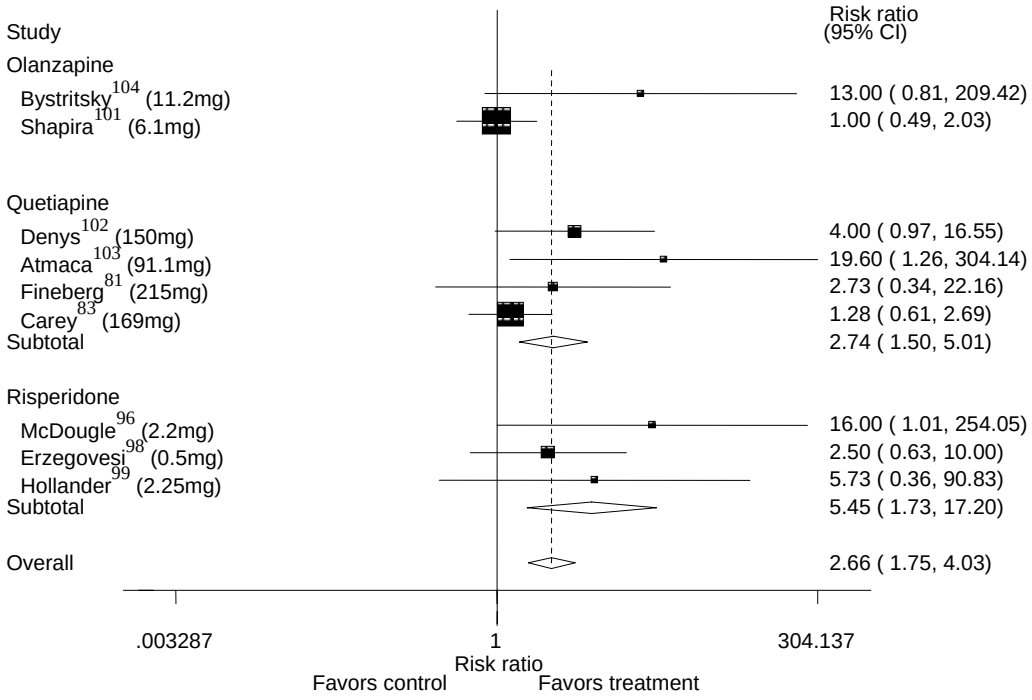
In summary, a moderate amount of evidence suggests that atypical antipsychotic medications have clinically important effects when used as augmentation therapy for 8 to 16 weeks for patients with OCD resistant to standard treatment. Only risperidone, olanzapine, and quetiapine have been studied. The evidence for benefit of risperidone and quetiapine is stronger than for olanzapine.

Table 4. Placebo-controlled trials of atypical antipsychotics as augmentation for obsessive compulsive disorder.

Author, Year Jadad Score	Subjects	N	Treatment	Primary Outcome	Duration
Erzegovesi, 2005[86] Jadad = 4	Fluvoxamine-refractory OCD patients (non-responders to 12 weeks of therapy)	20	Risperidone 0.5mg	Y-BOCS decrease of 35% or greater + CGI	6 weeks
Hollander, 2003[87] Jadad = 4	"Treatment-resistant" OCD: having failed at least 2 trials of SRI therapy. Required to be taking SRI for at least 12 weeks	16	Risperidone (average dose 2.25mg/day)	Y-BOCS decrease of 25% or greater + CGI	8 weeks
Bystritsky, 2004[92] Jadad = 3	"Refractory" OCD: having no improvement in at least 2 trials of SRI and at least 1 trial of behavioral therapy. Subjects had to be taking fluoxetine, paroxetine, or sertraline for at least 12 weeks.	26	Olanzapine (mean dose = 11-2mg/day)	Y-BOCS decrease of 25% or greater	6 weeks
Atmaca, 2002[91] Jadad = 2	"Treatment-resistant" OCD: at least one adequate SRI trial before a 3-month open-label trial of SRI; non-responders were selected.	27	Quetiapine (average dose = 91 mg /day)	Y-BOCS decrease of 30% or greater	8 weeks
Denys, 2004[90] Jadad = 4	"Refractory" OCD: failure on at least 2 treatments of SRI; all patients were currently taking SRI.	20	Quetiapine titration from 50 mg to 300 mg/day	Y-BOCS decrease of 35% or greater + CGI	8 weeks
Shapira, 2004[89] Jadad = 3	"Fluoxetine-refractory" OCD: 8-week trial of Fluoxetine, non-responders or partial responders were selected.	44	Olanzapine 5mg to 10 mg/day	Y-BOCS decrease of 25% or greater	8 weeks
McDougle, 2000[84] Jadad = 4	"Serotonin inhibitor-refractory" OCD, 12-week open-label SRI monotherapy, refractory patients were selected.	36	Risperidone (average dose = 2.2mg/day)	Y-BOCS 35% or greater and final score 16 or less + CGI	6 weeks
Fineberg, 2005[69] Jadad = 3	"Treatment-Resistant" OCD: at least 12 weeks of SRI treatment at maximum tolerated dose	21	Quetiapine (average dose = 215 mg/day)	Y-BOCS decrease of 25% or greater	16 weeks
Carey, 2005[71] Jadad = 4	OCD "Failure to respond adequately" to 12 week trials of SRI	42	Quetiapine (average dose = 169 mg/day)	Y-BOCS decrease of 25% or greater + CGI	6 weeks

Y-BOCS = Yale Brown Obsessive Compulsive Scale
CGI = Clinical Global Impression Scale

Figure 2. Pooled analysis of the effect of atypical antipsychotic medications versus placebo on "response" in patients with obsessive-compulsive disorder



P = 0.036 (chi-square test); I^2 = 51.6%

Posttraumatic Stress Disorder (PTSD)

Key Points

- We found four risperidone and two olanzapine trials of over six weeks for PTSD.
- There were 3 trials on men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety and overall symptoms when risperidone or olanzapine was used as augmentation therapy.
- We found 3 trials of atypical antipsychotics as monotherapy for women with PTSD; the evidence was inclusive regarding efficacy.
- We found no trials of quetiapine, ziprasidone, or aripiprazole.

Our literature search identified seven placebo-controlled trials of atypical antipsychotics for the treatment of PTSD. One RCT was excluded because the duration of the study was only 5 weeks (a minimum of 6 weeks was our threshold)[98]. Three of the remaining six RCTs assessed atypical antipsychotic treatment as augmentation therapy for men with combat-related PTSD; the

other three assessed atypical antipsychotics as monotherapy for patients with mixed or other forms of PTSD; these patients were almost exclusively women. In one trial,[73] women were allowed to enroll if they were on stable doses of one antidepressant and/or one hypnotic. Salient details of the placebo-controlled trials are presented in Table 5. Almost all trials were small, with only one study enrolling more than 21 patients. Four trials assessed risperidone; the other two trials assessed olanzapine. All trials were relatively short in duration, the longest being 16 weeks. In general, trials suggested benefits of atypical antipsychotics when used as augmentation therapy in men with combat-related PTSD. In contrast, results were mixed in the three small studies of atypical antipsychotics as monotherapy in women with mixed/other forms of PTSD.

The quality of evidence for use as augmentation therapy for combat-related PTSD in men is considered low, based on sparseness of data and that further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The quality of evidence for use as monotherapy in women with PTSD is considered very low, based on sparseness of data, heterogeneity, and that any estimate of effect is very uncertain.

Table 5. Posttraumatic Stress Disorder

AuthorYear, Jadad Score	Subjects	N	Treatments	Co-Treatments	Duration	Outcomes
Combat-Related PTSD						
Stein, 2002[99] Jadad = 3	Male veterans with chronic military-related PTSD (DSM-IV)	19	Olanzapine (mean dose=15 mg/day) vs. Placebo	SSRI	8 weeks	Statistically significant reduction in clinician-administered PTSD scale, Pittsburgh sleep quality index, CES-D, increase in weight (13.2 vs. -3.0 pounds)
Monnelly, 2003[100] Jadad = 4	Male combat veterans with DSM-IV criteria for PTSD and scored ≥20 on Cluster D subscale of the Patient Checklist for PTSD-Military Veterans	15	Risperidone (mean dose=0.57 mg/day) vs. placebo	Antidepressants, SSRIs, anti-anxiety agents	6 weeks	Statistically significant improvement on irritability symptoms, intrusive thoughts, and total scale for Patient Checklist-Military.
Bartzokis, 2004[45] Jadad = 3	Male veterans attending a VA residential psychosocial treatment program for PTSD	65	Risperidone (up to 3 mg/day) vs. placebo	Residential program, antidepressants, other psychotropic medication, anti-anxiety agents	16 weeks	Statistically significant improvement on HAM-A, PANSS-P, CAPS-D, CAPS-Total. No difference in side effects between groups
Other or Mixed PTSD						
Butterfield, 2001[101] Jadad = 3	Adults 18-70 attending a university psychiatry clinic or VA women's health center with DSM-IV criteria PTSD	15 (1 male)	Olanzapine (mean peak dose=14.1mg) vs. placebo	None reported	10 weeks	No difference in PTSD outcomes between groups. Weight gain was 11.5 lbs in the olanzapine group compared to 0.9 lbs with placebo.
Reich, 2004[73] Jadad = 2	Women with chronic PTSD due to childhood abuse. DSM-III-R criteria were used, with the SCID and CAPS PTSD scale. Patients needed to have a CAPS-1 score of ≥50	21	Risperidone (mean dose=1.41 mg) vs. placebo	No co-treatment with other antipsychotic or mood stabilizer was allowed	8 weeks	Significant benefits for risperidone-treated patients in CAPS-2 total score. Significant increases in prolactin in risperidone-treated patients.
Padala, 2005[72] Jadad = 2	Women with PTSD diagnosed with mini International Neuropsychiatric interview	20	Risperidone (mean dose=2.62 mg) v. placebo	No co-treatment allowed	11 weeks	A significant benefit for risperidone was observed only for some outcome measures with certain kinds of analysis.

Personality Disorders

Key Points

- Three RCTs, each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder.

- The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.

- Olanzapine caused significant weight gain in all studies.

- Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small nine week trial.

- Aripiprazole was more effective than placebo for the treatment of borderline personality in one small eight week trial.

- We found no studies of quetiapine of ziprasidone for personality disorders.

Our literature search identified six RCTs of atypical antipsychotics for the treatment of personality disorders. Five of these trials evaluated patients who met DSM-IV criteria for borderline personality disorder.[70, 102-105] Another RCT assessed risperidone in the treatment of schizotypal personality disorder.[106] Four of the RCTs were placebo-controlled,[102, 103, 105, 106] one study was an active-controlled trial,[104] and one studied the addition of olanzapine to dialectical behavior therapy.[70] Enrollment ranged from 26 to 60 subjects; the duration of trials ranged from eight weeks to 24 weeks. These trials were considered too clinically heterogeneous to justify pooling, hence our summary of the literature is narrative. Study details are presented in Table 6.

The first study assessed the effect of olanzapine versus placebo in 28 women.[103] The mean age was about 26 years, and most had been treated previously with psychotherapy or other psychotropic medications. Patients were randomized to olanzapine or placebo with dosing adjusted according to perceived response and side effects. The mean daily dose of olanzapine at the endpoint evaluation was 5.3 mg. Using random effects regression modeling (in an attempt to control for baseline values), the study found that olanzapine-treated patients had significantly greater improvements than placebo-treated patients in the Symptom Checklist-90 scales for interpersonal sensitivity, anxiety, anger/hostility, and paranoia. However, there were no differences in SCL-90 anxiety scores based on group means. Still, differences were more marked in the first 4 weeks.

The second study[102] also evaluated olanzapine versus placebo in the treatment of borderline personality disorder. In this study, 40 patients were randomized to receive increasing doses of olanzapine or placebo for 12 weeks. Twenty-three patients had at least one prior suicide attempt, and nine patients had a history of psychiatric hospitalization. Almost two-thirds of patients had a history of non-suicidal self-injurious behavior. The primary outcome was the total score for the nine DSM-IV borderline personality disorder criteria, each scored on a 1-7 Likert scale; the authors called this the *Clinical Global Impressions scale modified for borderline personality*

disorder. Using analysis of covariance, the study found statistically significant benefits for olanzapine treatment. Our calculation of standardized mean difference of change in CGI-BPD approached statistical significance. The effect was more pronounced in the first few weeks.

The third olanzapine trial[104] assessed the effect of olanzapine, fluoxetine, or the combination of olanzapine and fluoxetine in women. Forty-five women were randomized to either 10 mg fluoxetine or 2.5 mg of olanzapine or their combination, with the dose subsequently adjusted by an unblinded psychiatrist, according to perceived response and side effects. Subjects and raters were blinded to study assignment. The mean fluoxetine dose at eight weeks for subjects treated only with fluoxetine was 15 mg; and the mean does of olanzapine for olanzapine-treated subjects was 3.3 mg. In comparison, for the combination group, the mean dose of fluoxetine was 13 mg and that of olanzapine was 3.2 mg. Using random effects regression modeling, the study reported improvements in the modified overt aggression scale and the Montgomery-Asberg depression rating for patients. In general, symptomatically, patients on the combination of olanzapine and fluoxetine resembled those treated with olanzapine alone.

The fourth BPD trial assessed the effects of adding olanzapine to dialectical therapy on 60 patients.[70] All patients received dialectical therapy and were randomized to receive placebo or olanzapine at a flexible dose of 5 to 20 mg/day for 12 weeks. Almost 90 percent of enrolled subjects were women. Patients treated with olanzapine experienced a significant (two-point) improvement in the Hamilton Depression Score and a decrease in impulsive behavior compared with those on placebo.

Completion rates in the olanzapine trials ranged from about 50 percent to 93 percent. Mean weight gain in the olanzapine groups ranged from 1.29 to 8.9 kg; weight gain was always significantly higher than in the comparator groups. Mild sedation was common among olanzapine patients. No serious movement disorders were reported in any of the olanzapine groups.

The fifth trial assessed the effect of risperidone for the treatment of schizotypal personality disorder.[106] Twenty-five subjects with DSM-IV criteria for schizotypal personality disorder who did not meet current or lifetime DSM-IV criteria for schizophrenia or any schizophrenia-related psychiatric disorder or bipolar disorder were randomized after a single-blind, two-week, placebo lead-in period to either risperidone (titrated upward in a stepwise fashion) or placebo and then followed for 9 weeks. Most of the enrolled subjects were men, and the mean age was about 40. Most had comorbid personality disorders, usually paranoid, narcissistic, or avoidant. About 60 percent of subjects completed the trial. Risperidone-treated subjects experienced greater improvement on the Positive And Negative Syndrome Scale (PANSS) than did placebo controls. The risperidone group also had greater improvements on the Clinical Global Impression scale, the Hamilton Rating Scale for Depression, and the Schizotypal personality questionnaire than did the placebo group, but these improvements did not reach statistical significance. Side effects were reported by about half of the patients in each group. The authors concluded that low-dose risperidone appeared to be effective in reducing symptom severity in schizotypal personality disorder and was generally well tolerated.

The sixth trial assessed the effect of aripiprazole for the treatment of borderline personality disorder.[105] Fifty seven subjects (more than 80 percent female, mean age = 22) with DSM-IV criteria for borderline personality disorder were randomized to aripiprazole 15 mg/day or placebo. Subjects were followed for 8 weeks using the Symptom Checklist (SCL-90-R), the Hamilton Rating Scales for both Depression and Anxiety (HAM-D, HAM-A), and the State-Trait Anger Expression Inventory. Five subjects were withdrawn (groups not specified). On the SCL-

90-R and HAM-D subjects reported much greater reductions in depression, while reductions in anxiety on the HAM-A were more modest but still statistically significant. SCL-90-R domains that improved with aripiprazole more than placebo were obsessive-compulsive, insecurity in social contacts, aggressiveness/hostility, phobic thinking, paranoid thinking and psychoticism.

Summary

The modest size of the effect on most outcomes, the small size of the trials, the dropouts or loss to follow-up (in the majority of trials being 40 percent or greater), and the way the outcomes and statistical analyses were presented limit the ability to draw firm conclusions. The strength of evidence for all outcomes in this condition is very low due to sparseness of data and very serious limitations about study quality, with the result that any estimate of effect is very uncertain.

Table 6. Personality Disorders

Author, Year, Jadad score	Subject (s)	N	Treatment	Duration	Outcomes
Soler, 2005, 2	Borderline Personality Disorder, 90% women	60	Dialectical therapy + Placebo vs. dialectical therapy + Olanzapine, flexible dose	12 weeks	Change in HAM-D favoring Olanzapine SMD = 2.438 (1.765, 3.111); Change in CGI-S favoring Olanzapine WMD = -11.87(-14.226, -9.514)
Bogenschultz, 2004, 3	Borderline Personality Disorder, Age 18 to 54, 38% male	40	Placebo vs. Olanzapine Adjustable dosing	12 weeks	Change in CGI-BPD SMD = -.667 (-1.351, 0.018) No differences in SCL-90 scales.
Zanarini, 2001, 5	Borderline Personality Disorder, Females ages 18-40	28	Placebo vs. Olanzapine Adjustable dosing	24 weeks	Final change in SCL-90 anxiety disorder not significant between groups. Olanzapine group experienced faster rate of change in anxiety, paranoia, anger/ hostility.
Zanarini, 2004, 2	Borderline Personality Disorder, Females 18-40	45	Fluoxetine vs. Olanzapine vs. Olanzapine + Fluoxetine	8 weeks	Change in MADRAS not significant between groups.
Nichels, 2006, 4	Borderline Personality Disorder, 17% male, Age >=16	52	Placebo vs. Aripiprazole, 15mg fixed dose	8 weeks	Change in HAM-D, HAM-A, STAEI, and most of SCL-90 scales favoring aripiprazole
Koenigsberg, 2003, 4	Schitzotypal Personality Disorder, Age 18-60, 83% male	25	Placebo vs. Risperidone, up to 2 mg/day	9 weeks	Change in PANSS-TOTAL favoring risperidone - 1.624 (-2.595 to -0.653)

SMD = Standardized Mean Difference, WMD = Weighted Mean Difference
PANSS = Positive And Negative Syndrome Scale
MADRAS = Montgomery-Asberg Depression Rating Scale
HAM-D = Hamilton Depression Scale
SCL-90 = Symptom Checklist 90
CGI = Clinical Global Impression Scale

Tourette's Syndrome

Key Points

- We found four trials of risperidone and one of ziprasidone for this condition.
- The little evidence available is inconclusive about the efficacy of either drug.
- We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.

Our literature search identified five RCTs testing the effects of atypical antipsychotics in the treatment of children and adolescents with Tourette's syndrome.[107-111] Enrollment ranged from 19 to 51 subjects; length ranged from eight to 12 weeks. One RCT compared ziprasidone with placebo, another RCT compared risperidone with placebo,[108] and the other three RCTs compared risperidone with either pimozide or clonidine. Trial data is displayed in Table 7.

The first RCT was an 8-week placebo-controlled trial of ziprasidone in 28 patients, mostly male, ages 7-17 years (mean age 11).[107] Patients were randomized to receive either ziprasidone (starting at 5 mg and adjusted as tolerated to a maximum total daily dose of 40 mg, given as 20 mg twice daily) or placebo. Twenty-four patients completed the study. At 8 weeks, patients in the ziprasidone group experienced significant reductions when adjusted for pre-treatment values in the YGTSS Global Severity scores (decrease of 39 percent versus 16.2 percent, p=0.016) and total tic scores (decrease of 34.8 percent versus 6.9 percent, p=0.008). However, between group means were not significantly different. No significant differences were seen between groups in the Clinical Global Impression Severity scale scores. All 16 patients in the ziprasidone group and just over half of the patients in the placebo group experienced a "treatment-emergent" adverse event.

The second placebo-controlled trial assessed 34 patients, of whom 26 were children.[108] These patients were randomized to receive either risperidone at a titrated dose not to exceed 3 mg/day or placebo. After 8 weeks, the risperidone treated children experienced a significant reduction in YGTSS Total Tic scores (36 percent v. 9 percent reduction). Nine of 12 children treated with risperidone (compared with one of 14 treated with placebo) were deemed responders on the Clinical Global Impressions-Improvement measure.

The third trial compared risperidone with pimozide.[109] Patients up to age 50 were enrolled, however the median age was in the early 20s. Obsessive-compulsive symptoms were present in about half of patients in addition to Tourette's symptoms. Patients were randomized to receive either a fixed dose titration for the first week followed by flexible dosing for a period of 7 weeks or placebo treatment. The risperidone dose varied from 0.5-2.0 mg per day, and the pimozide dose varied from 1-2 mg per day. At the end of the study, both groups experienced significant improvements in the Tourette's syndrome severity scale and the Clinical Global Impressions scale, and there were improvements on most of the secondary outcomes, including the Hamilton rating scale for anxiety and the Yale-Brown Obsessive Compulsive Scale. However, there were no differences between groups in any of these outcomes. The authors report that younger patients in both groups had consistently better scores at baseline and at the endpoint but that overall age had little effect on the efficacy of either pimozide or risperidone.

The fourth RCT compared the effects of risperidone (mean dose 2.5 mg/day) with those of pimozide (mean dose 2.4 mg/day) in an 8 week crossover trial in 19 children with Tourette's or

chronic motor tic disorder (as defined in the DSM-IV-TR).[110] The dropout rate was approximately 33 percent. The YGTSS score was significantly lower during risperidone treatment than during pimozide treatment (42 percent decrease v. 16 percent decrease). No significant differences were found in Clinical Global Impression-Severity outcomes.

The fifth trial compared risperidone to clonidine in a RCT of 21 children and adolescents (90 percent male; average age 11).[111] Patients were randomized after completing a 7-14 day, single-blind, placebo lead-in to titrated doses of either risperidone or clonidine. The mean dose of risperidone at the end of the 8-week study was 1.5 mg per day, while the mean dose of clonidine was 0.175 mg per day. For the main outcome measures, which included the YGTSS, the Yale-Brown Obsessive Compulsive Scale, and the DuPaul Attention Deficit Hyperactivity Scale, both groups experienced significant improvements over time, but no significant differences were found between the drugs.

Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study; this was always more than the comparator groups. Weight gain with ziprasidone was similar to placebo. Transient mild sedation was common with ziprasidone. In addition, five boys in the ziprasidone group experienced above normal serum prolactin levels. Risperidone was well tolerated in the studies; adverse events included fatigue, somnolence, sedation, and stiffness.

Summary

Four small trials of risperidone provide evidence that it is more effective than placebo, and at least as effective as pimozide and clonidine, in children and adolescents with Tourette's syndrome for 8 to 12 weeks of therapy. Risperidone caused significant weight gain in these studies. The one available study of ziprasidone showed variable effectiveness compared to placebo. The strength of evidence for risperidone is low based on very sparse data and that future research is very likely to have an important effect on our confidence in the estimate of effect. For ziprasidone, the strength of evidence is very low based on sparseness and heterogeneity, and any estimate of effect is very uncertain.

Table 7. Tourette's Syndrome

Author, Year, Jadad score	Subjects	N	Treatment	Duration	Outcomes
Sallee, 2000, 3	Age 7 to 17, 79% male, severe tic symptoms, free of psychotropic meds 4 weeks	28	Ziprasidone 5 to 40 mg/day vs. Placebo	8 weeks	Ziprasidone group had significant reductions in Yale Global Tic Severity Scale compared to placebo. Differences in change in CGI-S not significant.
Scahill, 2003, 3	Age 6 to 62, 88% male	34 (26 children)	Risperidone vs. Placebo Adjustable dosing	8 weeks	Change in Yale Global Tic Severity Scale favors risperidone SMD = -1.090 (-1.814, -0.365), Also,more "responders" on CGI-I.
Bruggerman,2001, 5	Age 11 to 50, 88% male, 50% OCD symptoms	51	Pimozide vs. Risperidone, Flexible dosing	12 weeks	No significant differences between pimozide and risperidone in change in CGI, TSSS.
Gilbert, 2004, 5	Age 7 to 17, 79% male, severe tic symptoms	19	Crossover Pimozide vs. Risperidone, Adjustable dosing	12 weeks, cross at 4 weeks	Change in Yale Global Tic Severity Scale greater in risperidone at 4 weeks
Gaffney, 2002, 3	Age 7 to 17, 90% male	21	Clonidine vs. Risperidone, Adjustable dosing	8 weeks	No significant differences between clonidine and risperidone in change in Yale Global Tic Severity Scale, CGI.

TSSS = Tourette's Syndrome Severity Score
CGI = Clinical Global Impression Scale

Autism

Key Points

- In October 2006, the FDA approved the use of risperidone for autism.
- Two trials of eight weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism.
- We found no trials of olanzapine, quetiapine, ziprasidone or aripiprazole for this indication.

Our literature search identified reports of one open-label pilot study[112] and two placebo-controlled trials[113, 114] and one abstract[115] that reported on a subgroup analysis of one of the placebo-controlled trials[113] assessing use of atypical antipsychotics medications for children with autism.

The pilot study enrolled 12 children with the DSM-IV diagnosis of autistic disorder and randomized them to 6 weeks of open treatment with olanzapine or haloperidol;[112] it and was not included in our analyses due to small sample size.

The first placebo-controlled trial assessed the effect of risperidone in the treatment of children (81 boys and 20 girls; mean age approximately 9 years) who met DSM-IV criteria for autistic disorder.[113] Subjects were given increasing doses of risperidone to a maximum of 2.5 mg per day (mean 1.8 mg during the final week) and followed for 8 weeks. The primary outcome measure was the irritability subscale of the Aberrant Behavior Checklist. The study found improvement over time in both placebo- and risperidone-treated groups, with a significantly greater effect for risperidone than placebo (57 percent decrease versus 14 percent decrease, respectively; $p < 0.001$). With a "positive response" defined as a 25 percent improvement in the score on the irritability subscale and a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement Scale, 69 percent percent of risperidone-treated children were considered to have a "positive response" compared to 12 percent of placebo-treated children ($p < 0.001$). In a 6-month open-label extension, about two-thirds of patients who had a positive response in the double-blind phase of the study maintained these improvements. Improvements were seen in several secondary outcome measures as well. A greater mean increase in weight was seen in the risperidone group (2.7 kg) than in the placebo group (0.8 kg) ($p < 0.001$). However, no serious adverse events were found in the risperidone-treated group, and no child was withdrawn from the study because of an adverse event. The most common adverse events, in addition to increased appetite and weight gain, were drowsiness, fatigue, and nasal congestion. No extrapyramidal symptoms were observed in either group. The authors concluded that risperidone was safe and effective for the short-term treatment of tantrums, aggression, and self-injurious behavior in children with autistic disorder. In a subsequent paper, the same group of authors reported that risperidone was superior to placebo in reducing symptoms of most concern to the parents of these autistic children.[116]

The second placebo-controlled trial assessed the use of risperidone in 79 children (ages 5-12; average age 7 to 8; approximately 75 percent were male) who had a DSM-IV diagnosis of pervasive developmental disorder and a total score of 30 or more on the Childhood Autism Rating Scale.[114] About 70 percent of patients had a diagnosis of autistic disorder, with the

remainder having Asperger's disorder or other pervasive developmental disorders. Patients were randomized to a titrated dose of risperidone or placebo and followed for 8 weeks (final dose 1.5 mg/day). Both groups improved on the irritability subscale of the Aberrant Behavior Checklist, but the risperidone-treated children improved significantly more than the placebo group (64 percent versus 31 percent, respectively). As in the previous study, several secondary outcome measures also improved. The most common side effects reported for risperidone-treated children were somnolence, upper-respiratory tract infection, rhinitis, and increased appetite. The authors concluded that risperidone was effective for relieving many of the behavioral symptoms associated with pervasive developmental disorder in children.

Summary

Two placebo-controlled trials of moderate size and eight weeks duration reported consistent evidence that risperidone is superior to placebo in improving serious behavioral problems in children with autism. The quality of evidence for outcomes in this condition is considered low due to the sparseness of data, and that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Sensitivity Analysis

We conducted a sensitivity analysis on study quality. We extracted outcome data on 60 trials. Studies of better quality (as defined by scores of 3 or more on the Jadad scale) reported a 25 percent lower effect size than studies of lower quality, a result that was of borderline statistical significance (p=0.058).

The funding for 53 of the 60 trials for which we extracted outcome data (88 percent) was provided at least partly by the pharmaceutical industry, which precluded any assessment of differential effects associated with funding source. However, a recent relevant review of the relationship between industry sponsorship and the results of head-to-head trials of atypical antipsychotics (for all conditions) found that in 90 percent of such trials, the sponsor's drug was reported to be superior to the comparison.[93] This finding led to apparently contradictory conclusions about the superiority of one atypical antipsychotic over another, depending on the sponsorship of the trial. We presume this bias is also present for trials that compare a sponsor's drug to placebo. Therefore, the results of manufacturer-sponsored trials should be interpreted with caution.

We planned sensitivity analyses on dose and duration of treatment. However, these variables are condition-specific (and drug-specific in terms of dose) and too few trials were available within any one condition to support an analysis.

Publication Bias

The presence of possible publication bias was detected using the Begg's test and Eggar's test on the set of 60 studies for which we extracted effect sizes. Both tests yielded statistically significant results (p=0.001 or less). This finding indicates the presence of unexplained heterogeneity in trials. One possible source of heterogeneity is publication bias. Another potential explanation is that all the drugs do not work equally well for all conditions. It is not possible for us to more precisely determine the source of the heterogeneity. When assessed by

condition, only OCD yielded statistically significant test results (as reported previously and then in only one of two tests). However, the lack of statistical significance for either test cannot be construed to mean that publication bias does not exist. We assume that publication bias may be present for all conditions, resulting in an overestimation of the potential efficacy of these drugs for all conditions.

Key Question 3: What subset of the population would potentially benefit from off-label uses?

Key Point

There was insufficient information to answer this question. Therefore, it is included as a topic for future research.

Key Question 4. What are the potential adverse effects and/or complications involved with off-label antipsychotic prescribing?

Key Points

- There is high-quality evidence that olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics. In two pooled RCTs of dementia patients, olanzapine users were 6.12 times more likely to report weight gain than placebo users. In a head-to-head trial of dementia patients, olanzapine users were 2.98 times more likely to gain weight than risperidone patients. In two pooled RCTs for depression with psychotic features, olanzapine patients were 2.59 times as likely as those taking conventional antipsychotics to report weight gain.

- In a recently published meta-analysis of 15 dementia treatment trials, death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics versus 2.3 percent of patients randomized to receive placebo. The odds ratio for death was 1.54, with a 95 percent confidence interval of 1.06 to 2.23. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. Recent data from the DEcIDE Network suggest that conventional antipsychotics are also associated with an increased risk of death in elderly patients with dementia, compared to placebo.

- In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.

- In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo (OR 3.88, 95 percent CI 1.49 to 11.91). This risk was equivalent to one additional stroke for every 31 patients treated in this patient population, i.e., number needed to harm (NNH) of 31. The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone than in the placebo patients.

- In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.

- We pooled three aripiprazole trials and three risperidone trials which reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS (OR 2.53 and 2.82 respectively) compared to placebo. The number needed to harm was 16 for aripiprazole, and 13 for risperidone.

- In the CATIE trial, risperidone, quetiapine, and olanzapine were each more likely to cause sedation than placebo (15-24 percent vs. 5 percent), while olanzapine and risperidone were more likely to cause extrapyramidal signs than quetiapine or placebo (12 percent vs. 1-2 percent). Cognitive disturbance and psychotic symptoms were more common in olanzapine-treated patients than the others groups (5 percent vs. 0-1 percent).

- Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, or PTSD, or personality disorders (OR 3.32 95 percent CI 1.12 to 13.41).

- There is insufficient evidence to compare atypical with conventional antipsychotics regarding EPS or tardive dyskinesia in patients with off-label indications.

- Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Mean weight gain in the risperidone groups ranged from 2.1 kg to 3.9 kg per study. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.

- Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.

Detailed Analyses

One of the major rationales for preferring treatment with atypical antipsychotics over conventional antipsychotics is potentially greater safety. We examined adverse event data from all RCTs of atypical antipsychotics for off-label conditions, plus cohort studies and cases series with more than 1,000 subjects. To analyze the data from RCTs, we further divided them into

placebo-controlled trials, active-controlled trials, and head-to-head comparisons of atypical antipsychotics. We also discuss a recent meta-analysis of deaths in patients with dementia who were treated with atypical antipsychotics. A similar analysis led the FDA to issue a Public Health Advisory for treatment of dementia with atypical antipsychotics in 2005.

Of the 131 reports on RCTs, 119 reported adverse events. We excluded articles that reported data from a study already in the analysis (n= 26). Twenty trials did not report the appropriate count data, three did not report the data by treatment group, and three did not report on a comparison of interest. Thus, we extracted adverse event data from 67 RCTs. We also found 15 observational studies (case series and cohort) of more than 1,000 subjects. Five observational studies did not report the appropriate count data, three did not report the data by treatment group, and one did not report on a comparison of interest. Thus, we were able to include six observational studies in our adverse events analyses.

We identified and grouped the reports of adverse events into clinically relevant categories. These categories were then pooled within three condition categories, based on patient age. Patient age was a proxy measure for the baseline likelihood of adverse events; in other words, children, adults, and the very old are expected to have potentially different types of risks for adverse events. We analyzed studies of dementia patients separately (mean age = 80); pooled across the conditions of depression, obsessive-compulsive disorder, personality disorder, and PTSD (mean ages between 31 years and 46 years by conditions): and pooled across the conditions of autism (mean age = 7.8) and Tourette's (mean age = 18.2). We did not pool across drugs; instead we generated separate estimates for each of the five atypical antipsychotics. Separate analyses were conducted for placebo comparisons, active comparisons (comparing atypical antipsychotics to acetylcholinesterase inhibitors, benzodiazepines, clonidine, conventional antipsychotics, mood-stabilizers, SRIs, and tricyclic antidepressants), and the few head-to-head trials of atypical antipsychotics. We also analyzed a few studies that compared an atypical added to a conventional therapy (for example, studies of an SRI versus an SRI plus an atypical antipsychotic).

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

Dementia

Our adverse events analyses for dementia included 13 placebo-controlled trials, six active-controlled trials, five head-to-head trials, and three observational studies.

In the placebo-controlled trials (PCTs), olanzapine was statistically associated with increases in appetite/weight (OR 6.12, 95 percent CI: 1.49 to 54.04, NNH = 19), as well as anticholinergic events (OR 3.29, 95 percent CI: 1.62 to 7.17, NNH = 5). In the CATIE trial, patients with dementia who were treated with olanzapine, quetiapine or risperidone averaged a monthly weight gain of 1.0, 0.7 and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month.

The group of symptoms which we categorized as cardiovascular (including "cardiovascular symptoms," "edema," and "vasodilation") was reported significantly more often in patients taking olanzapine or risperidone than in those taking placebo (OR of 3.31 and 2.33 respectively).

The number needed to harm was 25 for olanzapine and 16 for risperidone. Cerebrovascular accident (CVA) was reported in three placebo-controlled trials of risperidone; the drug was associated with an increase in CVA. Number needed to harm was 31. Aripiprazole and olanzapine were not associated with an increase in CVA in the trials of each where CVA was reported. No trials of quetiapine or ziprasidone reported CVA. Table 8 displays our analyses.

Table 8. Cardiovascular adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Cardiovascular/CVA	Olanzapine	2	2	232	5	278	2.09	(0.32, 23.27)	NC	NC
Cardiovascular/CVA	Risperidone	3	6	550	21	487	3.88	(1.49, 11.91)	31	(19, 82)
Cardiovascular – other	Olanzapine	4	5	298	38	678	3.31	(1.27, 10.91)	25	(16, 60)
Cardiovascular – other	Risperidone	4	27	665	110	1060	2.33	(1.48, 3.78)	16	(12, 25)

NC = Not calculated

To analyze extrapyramidal side effects (EPS), we were able to pool three PCTs for aripiprazole and four PCTs for risperidone. Both drugs were associated with an increase in EPS (OR 2.53 and 2.82 respectively) compared to placebo. The NNH for aripiprazole was 16, for risperidone 13. There was insufficient EPS data to pool for olanzapine, quetiapine, and ziprasidone.

Risperidone, olanzapine and aripiprazole were each associated with sedation in dementia PCTs. The NNH ranged from eight to ten. Table 9, below, displays analyses on neurological side effects.

Table 9. Neurological adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Neuro/Movement Disorder/EPS	Aripiprazole	3	16	348	39	359	2.53	(1.34, 5.01)	16	(10, 42)
Neuro/Movement Disorder/EPS	Risperidone	4	29	713	114	949	2.82	(1.81, 4.51)	13	(10, 18)
Neuro/Movement Disorder/Gait	Olanzapine	4	15	373	79	641	2.75	(1.52, 5.79)	12	(9, 20)
Neuro/Movement Disorder/Gait	Risperidone	3	8	406	32	448	3.04	(1.32, 7.84)	19	(13, 41)
Neuro/Movement Disorder/ Tardive Dyskinesia	Risperidone	3	14	475	4	714	0.31	(0.07, 1.03)	NC	NC

Neuro/Sedation	Aripiprazole	3	10	348	54	359	6.68	(3.19, 15.72)	8	(6, 12)
Neuro/Sedation	Olanzapine	5	24	440	152	778	4.26	(2.66, 7.08)	8	(6, 12)
Neuro/Sedation	Risperidone	6	87	922	249	1260	2.50	(1.89, 3.34)	10	(8, 13)

NC = Not Calculated

Olanzapine, risperidone, and aripiprazole were each associated with a significant increase in the constellation of symptoms we categorize as other neurological (including "confusion," "dizziness," "dizziness and headaches," "lightheadedness," "orthostatic dizziness," "seizure," and "tinnitus"). Aripiprazole, olanzapine, and risperidone were associated with an increase in fatigue (OR of 3.67, 2.37, and 3.56, respectively). The latter two drugs were also associated with gait disorders in dementia patients.

Urinary symptoms were significantly more common in dementia patients treated with aripiprazole and risperidone than with placebo (OR of 4.07 and 1.55 respectively). There was insufficient data to conduct analysis for ziprasidone or quetiapine.

Table 10. Urinary adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	**Drug**	**# of studies**	**# adverse events**	**sample size**	**# adverse events**	**sample size**	**Pooled OR**	**95% CI**	**NNH**	**95% CI NNH**
Urinary	Aripiprazole	3	45	348	115	359	4.07	(2.61, 6.44)	5	(4, 8)
Urinary	Risperidone	4	71	665	164	1060	1.55	(1.13, 2.13)	21	(13, 63)

In a trial of risperidone versus acetylcholinesterase inhibitors in 27 dementia subjects, risperidone patients had significantly fewer gastro-intestinal events. A trial of olanzapine versus benzodiazepines in 205 patients showed no significant difference in adverse events.

In a very small trial of risperidone and olanzapine versus conventional antipsychotics (n = 40), no patients on atypicals reported decreased salivation, compared to six subjects on conventional antipsychotics. Fewer olanzapine subjects reported blood pressure decrease and cardiovascular rhythm irregularities in this trial.

Adverse events were analyzed in one trial that compared risperidone plus rivastigmine to rivastigmine alone. While several events were noted in these dementia patients, the risks did not differ significantly between treatment groups.

In two head-to-head dementia studies, olanzapine subjects had significantly higher odds of weight gain or increase in appetite (OR 2.98, 95 percent CI:1.08 to 9.50) than risperidone subjects. In one head-to-head trial, a risperidone subject reported a pulmonary adverse event, compared with no subjects in the olanzapine group.

Recently, the Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease (CATIE-AD) trial was published; 4 compared olanzapine, quetiapine, and risperidone to each other and to placebo.[19] The design of this trial is discussed in more detail earlier. In terms

of adverse events, all three atypical antipsychotics were more likely to cause sedation than placebo (15-24 percent vs. 5 percent), while olanzapine and risperidone were more likely to cause extrapyramidal signs than quetiapine or placebo (12 percent vs. 1-2 percent). Cognitive disturbance and psychotic symptoms were more common in olanzapine-treated patients than the others groups (5 percent vs. 0-1 percent). Weight gain was greatest in the olanzapine group (gain of 1.0 pound per month vs. gain of 0.4 - 0.7. pound per month).

Observational studies of dementia patients found that olanzapine patients had lower odds of CVA than quetiapine patients (OR 0.83) or risperidone patients (OR 0. 71). However, these results did not meet conventional levels of statistical significance (95 percent CIs: 0.65 to 1.06, 0.45 to 1.11). Risperidone patients had higher odds of CVA than untreated patients (OR 1.35, 95 percent CI: 1.07 TO 1.71).

In two trials of aripiprazole, dermatologic problems were significantly more likely than in patients taking placebo (OR 2.53, 95 percent CI: 1.54 to 3.62, NNH = 6).

Meta-Analyses of the Effect of Atypical Antipsychotic use on the Risk of Death and Other Side Effects in Patients with Dementia

A meta-analysis of atypical antipsychotic medication use and death in Alzheimer's disease patients was recently published.[14] This meta-analysis included both published and unpublished randomized placebo-controlled parallel group clinical trials of atypical antipsychotics. Fifteen RCTs were included (eight were cited only as abstracts): four trials of risperidone, five trials of olanzapine, three trials of quetiapine, and three trials of aripiprazole. In all, 3,353 patients received an atypical antipsychotic, and 1,757 received placebo. With one exception, trials lasted from 6-12 weeks. (The one exception was 26 weeks.) Death occurred in 118 or 3.5 percent of patients randomized to receive atypical antipsychotics versus 40 or 2.3 percent of patients randomized to receive placebo. The odds ratio for death using a fixed effects model was 1.54, with a 95 percent confidence interval of 1.06 to 2.23. The difference in risk for death was small but statistically significant ($p = .01$). In other words, the number needed to harm was 100, although the 95 percent confidence intervals were broad. Pooled data from 2 trials containing a haloperidol treatment arm indicated that treatment with this conventional antipsychotic was also associated with a similar, albeit not statistically significant, increase in death. The authors concluded that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. A very similar analysis performed by the FDA was sufficient for the FDA to issue a 2005 Public Health Advisory regarding the use of atypical antipsychotics in elderly persons with dementia. Other reports attribute the increased risk of death to cerebrovascular events.[117, 118]

These authors also published the effectiveness meta-analysis discussed earlier[13]. They reported that adverse events were inconsistently reported among trials and that most did not report adverse events that occurred less than 5 percent or 10 percent of the time, meaning potentially significant adverse events may have been left out. Somnolence was consistently identified as a statistically significant increased risk, with an odds ratio of 2.84. No effect was seen on accidental injury or falls. Compared with placebo, extrapyramidal effects were more common in risperidone-treated patients but not in patients treated with other atypical antipsychotics. Data from a small number of trials showed an increased risk of abnormal gait. In placebo controlled trials of risperidone and olanzapine, there was increased risk of edema.

Compared with placebo, cardiovascular adverse events were more common in risperidone-treated patients, and in patients treated with atypical antipsychotics overall.

After we completed our analyses, the manufacturers of olanzapine published an analysis comparing that drug to placebo, risperidone, and conventional antipsychotics in elderly patients with dementia.[119] They reviewed six controlled trials and found that the incidence of mortality was significantly higher in olanzapine patients than in those treated with placebo. Differences in mortality between olanzapine and risperidone were not statistically significant; nor were differences between olanzapine and conventional antipsychotics. Incidence of cerebrovascular adverse events (hemorrhagic strokes, ischemic strokes, cerebrovascular accidents, or transient ischemic attacks) was three times higher in olanzapine patients than in the placebo patients; differences between olanzapine and risperidone and olanzapine and conventional antipsychotics were not significant.

As this report was being finalized, three abstracts from AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program were made available. Each of the studies used health care utilization data for British Columbia adults aged 65 years or older to assess the association between use of conventional antipsychotics, atypical antipsychotics, and death. Users of conventional antipsychotics had a 35 percent increased mortality risk compared to atypical antipsychotics users; this increase was attributable to increased fatal out-of-hospital cardiac events, pneumonia, and stroke.[120-122]

Children/Adolescents with Tourette's Syndrome or Autism

Our adverse events analyses for Tourette's syndrome and autism included four placebo-controlled trials and three active-controlled trials. There were no head-to-head trials or observational studies with usable data for these conditions.

Results showed several statistically significant differences between atypical antipsychotics and placebo. With risperidone, weight gain was 5.94 times more likely (95 percent CI: 2.94 to 12.62, NNH = 4) and decreased blood pressure was 12.47 times more likely than with placebo (NNH = 9). However, the confidence interval for decreased blood pressure was very wide (95 percent CI: 1.75 to 547.58). Odds were 3.24 times higher for gastrointestinal problems (95 percent CI: 1.41 to 7.92) and 5.35 times higher for increased salivation with risperidone. Risperidone subjects also had higher odds than placebo subjects for fatigue (OR 4.40; 95 percent CI: 2.04 to 9.94), extrapyramidal effects (OR 4.85, 95 percent CI: 2.15 to 12.08), and sedation (OR 12.09; CI: 5.40 to 29.61).

The one placebo-controlled trial of ziprasidone had only 28 patients and showed no significant difference in adverse events between groups.

A study comparing risperidone with clonidine had only 17 subjects and showed no significant differences in adverse events between groups. Olanzapine and risperidone were each compared with conventional antipsychotics in one trial; fewer risperidone patients had sleep disorders.

Depression, OCD, PTSD, Personality Disorders

Our adverse events analyses for these conditions included 20 placebo-controlled trials, 13 active-controlled trials, three head-to-head trials, six augmentation trials, and three observational studies.

In the placebo-controlled trials (PCTs), olanzapine was statistically associated with increases in appetite/weight gain (OR 11.16, 95 percent CI: 7.40 to 17.24). In one small PCT of risperidone, three out of 20 subjects in the treatment group reported weight gain, compared with no placebo subjects. In one PCT of ziprasidone, two out of 210 treatment subjects reported weight gain, compared with no placebo subjects.

Regarding cardiovascular symptoms, in one PCT (N = 201) seven olanzapine subjects reported them, compared with no placebo subjects. In a PCT of ziprasidone (N= 139), two treatment subjects reported them, compared to no placebo subjects.

Decreased salivation was significantly more common in subjects taking olanzapine and quetiapine than placebo (ORs 2.71 and 8.90, respectively). In two PCTs, liver function test abnormalities were more common in patients taking olanzapine (12 of 171 treated patients compared to none of 169 placebo patients). In a PCT of ziprasidone, one treatment subject had an abnormal liver function test; no one in the placebo group did.

When compared to placebo, all atypical antipsychotics were associated with an increase in at least some symptoms categorized as neurological ("confusion," "dizziness," "headaches," "lightheadedness," "orthostatic dizziness," "seizure," and "tinnitus"). Specifically, ziprasidone was associated with a significant increase in extrapyramidal side effects (OR 3.32, 95 percent CI: 1.12 to 13.41). All atypicals except aripiprazole were significantly associated with sedation; NNHs ranged from 2 to 6. In three studies that reported on headache, olanzapine subjects had lower odds of headache than placebo subjects (OR 0.69, 95 percent CI: 0.48 to 0.98). In one PCT of aripiprazole, five treatment subjects reported akathisia compared to no placebo subjects. Olanzapine was significantly associated with fatigue (OR 2.98, 95 percent CI: 1.72 to 5.35). One PCT each of risperidone and ziprasidone reported numbers for fatigue: No placebo subjects reported fatigue compared to one risperidone subject and three ziprasidone subjects.

One large observational study reported lower odds of diabetes in risperidone subjects than in placebo subjects (OR= 0.21, 95 percent CI: 0.07 to 0.51). There was no difference between placebo and olanzapine or quetiapine in diabetes rates.

Adverse event reports for the atypical antipsychotic medications were compared to those for conventional antipsychotics, mood stabilizers, SRIs, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRIs). Olanzapine had a significantly higher risk of sedation than both mood stabilizers and SRIs (OR 2.81, 95 percent CI: 1.59 to 5.07 and OR 6.04, 95 percent CI: 1.95 to 22.41). Olanzapine had a significantly lower risk for sleep disorders than did mood stabilizers (OR 0.43, 95 percent CI: 0.25 to 0.75). One study reported that ziprasidone had higher odds of causing gastrointestinal disorders, general neurological disorders, fatigue, agitation, and sleep disorders than did SRIs.

We were able to compare adverse events in conventional versus atypical antipsychotics in a couple of trials and observational studies. In two pooled studies, weight gain was more common among olanzapine patients than those taking conventional antipsychotics (OR 2.59, 95 percent CI: 2.02, 3.34). In one large observational study, olanzapine patients were less likely to observe cardiovascular symptoms, fever / infection, gastrointestinal, musculoskeletal, and constitutional problems. Olanzapine patients were also less likely to experience the neurological symptoms fatigue, akathisia, extrapyramidal side effects, and sedation in this study. In one trial of aripiprazole versus conventional antipsychotics, fewer aripiprazole patients experienced akathisia (OR 0.44, 95 percent CI: 0.33, 0.60) and extrapyramidal side effects (OR 0.24, 95 percent CI: 0.18, 0.32).

Examining the head-to-head trials, we found that few adverse events were reported in more than one study. Olanzapine was associated with a higher occurrence of weight gain but a lower occurrence of psychotic events, when compared to ziprasidone. Olanzapine had a higher risk for precipitating diabetes than did risperidone. When compared with risperidone, quetiapine had higher odds of decreased salvation, neurological events, sedation, and agitation.

Six studies compared an atypical antipsychotic plus a conventional drug to the conventional drug alone. In two studies, quetiapine administered with an SRI had a significantly higher risk of producing sedation than did the SRI alone (OR 9.32 95 percent CI: 2.16, 58.89). In one study, quetiapine plus paroxetine had lower odds of anxiety and sleep disorders than paroxetine alone. In one study of 36 subjects, five subjects taking the SRI alone reported headaches compared to none taking the SRI plus risperidone. 17 of the 20 patients taking the SRI plus risperidone reported sedation, compared to 8 of 16 taking the SRI alone.

Schizophrenia

Because of the paucity of data directly comparing adverse events among atypical antipsychotics prescribed for off-label uses outside of dementia, we reviewed the results of the CATIE trial, a multi-center study at 57 US sites that randomized 1,493 patients with chronic schizophrenia (the indicated condition for these drugs) to receive either olanzapine, quetiapine, risperidone, ziprasidone, or the conventional antipsychotic, perphenazine.[123] This study found that risperidone had the lowest rate of treatment discontinuation due to intolerable side effects (10 percent), whereas olanzapine had the highest rate (18 percent). More patients treated with perphenazine discontinued treatment due to extrapyramidal effects than did those treated with any of the atypical antipsychotics (8 percent vs. 2-4 percent). However, there were no significant differences among the groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders, as measured by the AIMS Global Severity Score, the Barnes Akathisia Rating Scale, or the Simpson-Angus Extrapyramidal Signs Scale. Weight gain was more common in patients treated with olanzapine (average weight gain of two lbs. per month) than in other patients. Two to three times as many patients in the olanzapine-treated group gained 7 percent or more of their baseline body weight as in the other groups. More patients discontinued therapy with olanzapine due to weight gain or metabolic effects than those treated with other drugs (9 percent vs. 1-4 percent). Adverse changes in glycosylated hemoglobin, cholesterol, and triglycerides were also more likely in olanzapine-treated patients than in those treated with the other drugs, while changes in blood glucose level were also greater in olanzapine-treated patients, but the difference did not reach statistical significance. Only risperidone was associated with increasing prolactin levels. Quetiapine treated patients had higher rates of anticholinergic effects (such as dry mouth) than the other drugs, whereas patients treated with olanzapine or quetiapine had lower rates of insomnia than did patients in the other groups. Although the CATIE trial has been critiqued for the dropout rate and the perception that the dose of olanzapine used was comparatively higher than the dose for the other atypical antipsychotics, these data support the findings from the clinical trials of atypical antipsychotics for off-label indications that olanzapine causes the most weight gain but is associated with lower rates of insomnia and that treatment with atypical antipsychotics results in fewer extrapyramidal side effects and movement disorders than does treatment with conventional antipsychotics.

Tardive dyskinesia is a potentially irreversible long-term adverse effect of treatment with conventional antipsychotics. Because the development of tardive dyskinesia is associated with

extrapyramidal side effects, and these side effects are less common among patients treated with atypical antipsychotics, tardive dyskinesia itself is believed to be less common in patients treated with the atypicals. In general the RCTs reviewed in this evidence report were of insufficient duration to detect differences in the rates of development of tardive dyskinesia (there were only six RCTs of at least 1 year's duration). In the CATIE study (reviewed above), which followed patients for 18 months, there was no difference among atypical antipsychotics or between atypical antipsychotics and perphenazine in the Abnormal Involuntary Movement Scale (AIMS) Global Severity score.[123] However, a systematic review of RCTs of atypical antipsychotics that lasted at least 1 year and that reported on new cases of tardive dyskinesia or dyskinesia concluded, based on 11 trials that assessed risperidone, olanzapine, quetiapine, amisulpride, or ziprasidone and involved a total of 2,769 patients, that the weighted-mean annual incidence of tardive dyskinesia for the atypical antipsychotics was 0 percent in children, 0.8 percent in adults, 6.8 percent in a mixed population of adults and elderly, and 5.3 percent in patients 54 years of age and older.[124] In comparison, the weighted-mean annual tardive dyskinesia risk for haloperidol in three RCTs involving adults was 5.4 percent. Statistical testing of differences between groups was not performed in this meta-analysis. However, we performed our own fixed-effects pooled analysis of two of the three RCTs that directly compared an atypical antipsychotic to haloperidol. Our pooled analysis yielded an odds ratio of 0.40 (95 percent CI: 0.22, 0.72), meaning that the atypical antipsychotic medications were significantly less likely to lead to tardive dyskinesia. However, the authors of the meta-analysis note that in the three RCTs that compared atypical antipsychotics with haloperidol, the doses of haloperidol were higher than generally considered appropriate. The authors concluded that these data support the hypothesis that second generation antipsychotics have a lower risk of tardive dyskinesia than first generation antipsychotics at higher doses but called for more carefully designed trials.[124] A recent trial, available in abstract form only,[74] reported that among 293 highly selected patients who primarily had dementia with agitation (of whom only about half completed the trial), those randomized to olanzapine had a lower rate of developing persistent tardive dyskinesia than patients randomized to conventional antipsychotic therapy for up to 1 year (2.5 percent vs. 5.5 percent, respectively), although this difference was not statistically significant (p= 0.204). These results agree well with our pooled analysis that the atypical antipsychotics have an odds ratio for developing tardive dyskinesia that is about half that of conventional antipsychotics.

Summary

In summary, there is consistent high-quality evidence across multiple trials that olanzapine is associated with more weight gain than placebo, typical antipsychotics, or other atypical antipsychotics. Evidence about weight gain for other atypical antipsychotics is not as robust.

There is also moderate-grade evidence from multiple trials that the atypical antipsychotics are associated with a greater risk (compared with placebo) of the constellation of symptoms such as confusion, dizziness, somnolence, and sedation.

Although the evidence from off-label uses is insufficient to draw conclusions, limited evidence from patients with schizophrenia suggests that atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol. The grade of evidence for this outcome is low. There is moderate to strong evidence that most atypical antipsychotics are associated with an increase in extrapyramidal signs or symptoms (excluding tardive dyskinesia) relative to placebo. The CATIE-AD trial concluded that EPS are more common with olanzapine

and risperidone than quetiapine. There is also low-grade evidence that, in adults, the atypical antipsychotics aripiprazole and olanzapine are associated with a lower risk of extrapyramidal side effects than are conventional antipsychotics.

There is moderate-quality evidence from meta-analyses that the use of atypical antipsychotics is associated with an increased risk of death in elderly patients with dementia and agitation. Although these results come from numerous RCTs that are all direct and consistent, this outcome receives this grade because we expect further research is likely to have an important impact on our confidence in the estimate or effect and may change the estimate. For risperidone and olanzapine, this outcome may be due to an increased risk of stroke. Conventional antipsychotic drugs also increase the risk of death in similar patients; however, the grade of evidence for this outcome is low. Other differences in adverse events/safety between atypical antipsychotics and conventional antipsychotics or placebo were either small or inconsistent.

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

Key Point

There was insufficient information to answer this question. Therefore, it is included as a topic for future research

Summary and Discussion

In this chapter, we describe the limitations of our review and meta-analysis and then present our conclusions. We also discuss the implications of our findings for future research.

Limitations

Publication Bias

Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, our test for possible publication bias indicates that there is unexplained heterogeneity, one reason for which could be publication bias. Furthermore, when we reviewed the recent meta-analysis assessing death and the use of these drugs in persons with dementia, we learned of the existence of some manufacturer-supported trials, the published results of which we searched for and were not able to find, despite extensive computerized searches and requests to the manufacturers (we have since learned the results were not published). It is possible that other such unpublished trial results exist for the other conditions included in our report. We assume that publication bias may occur for all conditions, resulting in an overestimation of the efficacy of these drugs for all conditions.

Study Quality

An important limitation common to systematic reviews is the quality of the original studies. Recent attempts to define elements of study design and execution that are related to bias have shown that in many cases, such efforts are not reproducible and do not distinguish studies based on result bias. Therefore, the current approach is to avoid rejecting studies or using quality criteria to adjust the meta-analysis results. However, we did use as a measure of quality the Jadad scale, which is the only validated set of quality criteria for trials. As there is a lack of empirical evidence regarding other study characteristics and their relationship to bias, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. Even given this limitation, our sensitivity analysis on the relationship between trial quality (as measured using Jadad's scale) and result leads us to conclude that the better quality trials report an effect size 25 percent smaller than do lower quality trials. This finding increases the likelihood that a synthesis of results of all studies - whether narrative or quantitative - is producing inflated estimates of efficacy.

Heterogeneity

In our meta-analysis, we observed evidence of heterogeneity. In an attempt to incorporate any heterogeneity, we used a random effects approach. There were too few trials to perform sensitivity analyses using variables that might account for heterogeneity other than quality (completeness of follow-up, dose, etc.). Further, we are unable to explain most of the heterogeneity. Thus, our pooled results should be interpreted in light of the observed heterogeneity.

Applicability of Findings

Green & Glasgow[125] provide a framework for evaluating the relevance, generalization, and applicability of research. Their framework includes assessing the participation rate, the intended target population, representativeness of the setting, representativeness of the individuals, along with information about implementation and assessment of outcomes. As these data are reported rarely in the studies we reviewed, conclusions about applicability are necessarily weak. In many cases, enrollment criteria for these trials were highly selective (for example, requiring an open-label run in). Such highly selective criteria many increase the likelihood of benefit and decrease the likelihood of adverse events in such patients. At best we judge these results to be only modestly applicable to the patients seen in typical office-based care.

Conclusions

With the above limitations in mind, we reached the conclusions displayed in the table below.

Table 11. Summary of evidence- efficacy

Condition	Strength of Evidence	Conclusion
Behavioral Problems in Dementia	Moderate for risperidone, olanzapine, and quetiapine; low for aripipipazole.	• A recent meta-analysis of 15 placebo-controlled trials found a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes. • Evidence from this meta-analysis shows a trend toward effectiveness of olanzapine for psychosis; results did not reach statistical significance. The authors found three studies of quetiapine; they were too dissimilar in their design and outcomes to pool. • A large head-to-head placebo controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease; CATIE-AD) concluded there were no differences in time to discontinuation of medication between risperidone, olanzapine, quetiapine and placebo. Efficacy outcomes favored risperidone and olanzapine, and tolerability outcomes favored quetiapine and placebo. • We found no studies of ziprasidone for agitation and behavioral disorders in elderly persons with dementia.
Specific Categories of Depression: **a. Inadequate Response to SRI** **b. with psychotic features** **c. with bipolar disorder**	Moderate that olanzapine whether used as monotherapy or to augment therapy does not improve outcomes at 8 weeks in SRI resistant depression; low for all atypical antipsychotics for other depression indications, due to small studies, inconsistent findings or lack of comparisons to usual treaments.	• For serotonin reuptake inhibitor (SRI)-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone, at 8 weeks. • In two trials enrolling patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxentine were compared with placebo for 8 weeks. Neither trial indicated a benefit for olanzapine alone. In one trial, the combination group had significantly better outcomes than placebo or olanzapine alone, but the contribution of olanzapine cannot be determined as the trial lacked a fluoxetine-only comparison arm. • For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies which compared atypical antipsychotics to conventional therapy. • We found no studies of aripiprazole for depression.

Condition	Strength of Evidence	Conclusion
Obsessive-Compulsive Disorder	Moderate for risperidone and quetiapine; low for olanzapine due to sparse and inconsistent results.	• We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients with OCD who were resistant to standard treatment. • A moderate amount of evidence from nine trials shows that these drugs have a clinically important beneficial effect when used as augmentation therapy for patients who failed to adequately respond to SRI therapy. • We found no trials of ziprasidone or aripiprazole for obsessive-compulsive disorder.
Post-traumatic Stress Disorder	Low for risperidone for combat-related PTSD due to sparse data; very low for risperidone and olanzapine for treating PTSD due to causes other than combat.	• We found four risperidone and two olanzapine trials of over six weeks for PTSD. • There were 3 trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. • We found 3 trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy. • We found no studies of quetiapine, ziprasidone, or aripiprazole for PTSD.
Personality Disorders	Very low due to small effects, small size of studies, and limitations of trial quality.	• Four RCTs, each with no more than 60 subjects, provide evidence that olanzapine is more effective than placebo and may be more effective than fluoxetine in treating borderline personality disorder. • The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small. • Olanzapine caused significant weight gain in all studies. • Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small 9- week trial. • Aripiprazole was more effective than placebo for the treatment of borderline personality in one small 8-week trial.
Tourette's Syndrome in Children / Adolescents	Low for risperidone; very low for ziprasidone.	• We found four trials of risperidone and one of ziprasidone for this condition. • The little evidence available is inconclusive about the efficacy of either drug. • We found no studies of aripiprazole, quetiapine, or olanzapine for Tourette's symptoms.
Autism in Children / Adolescents	Low for risperidone due to sparse data.	• Just before this report was published, the FDA approved risperidone for use in autism • Two trials of eight weeks duration support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism. • We found no trials of olanzapine, quetiapine, ziprasidone or aripiprazole for autism.

Table 12. Summary of adverse event and safety findings for which there is moderate or strong evidence

Side effect	Head to head trials	Active control trials	Placebo controlled trials
Mortality (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for atypical antipsychotics compared to placebo.
Cardiovascular (not including cerebrovascular accident)	Insufficient evidence of difference.	Insufficient evidence of difference.	Insufficient evidence of difference.
Cerebrovascular accident (dementia patients only)	Insufficient evidence of difference.	Insufficient evidence of difference.	Small but significant increased risk for risperidone and olanzapine compared to placebo.
Extrapyramidal symptoms	More common in olanzapine and risperidone than in quetiapine.	Insufficient evidence of difference.	More common in risperidone, olanzapine, aripiprazole, and ziprasidone than placebo, quetiapine insufficiently studied.
Neurological (fatigue, headaches, dizziness; excludes movement disorders)	Insufficient evidence of difference.	Insufficient evidence of difference.	More common in risperidone, olanzapine and aripiprazole than placebo, other drugs insufficiently studied.
Sedation	Insufficient evidence of difference	More common in olanzapine than mood stabilizers.	More common in atypical antipsychotics than placebo.
Weight gain	More common in olanzapine than other atypical antipsychotics.	More common in olanzapine than conventional antipsychotics.	More common in olanzapine and risperidone than placebo, other drugs insufficiently studied.

Future Research

More research is urgently needed about how to safely treat agitation in dementia. We make this statement based on the prevalence of the condition and uncertainty about the balance between risks and benefits in these patients. While the reported increase in risk of death in patients treated with atypical antipsychotics was small, the demonstrable benefits in the RCTs we identified were also small. Furthermore, we need to understand whether the increased risk of death is associated with all antipsychotics drugs. Recent observational studies from the DEcIDE program suggest that typical (conventional) antipsychotics may have an even greater risk than atypical antipsychotics. Part of this research program is going to require new clinical trials that measure benefit and are also appropriately powered to detect an increased risk of death - which will require very large sample sizes. Without measuring this risk of death in the same trials used to measure benefit, we will continue to be forced to rely on indirect--rather then direct--methods to compare risks and benefits. The results of the CATIE-AD study have added substantially to our knowledge about use of atypical antipsychotics in patients with dementia. We await the results of phase 2 of CATIE-AD.

Related to the above question, but not limited to dementia per se, is the need for studies comparing the development of extrapyramidal symptoms--particularly tardive dyskinesia--between patients taking atypical antipsychotics and those taking typical doses of conventional antipsychotics. Understanding how drug dose and age influence the occurrence of death or extrapyramidal symptoms/tardive dyskinesia would help estimate possible risks in specific populations.

With few exceptions, there is insufficient high-grade evidence to reach conclusions about the efficacy of atypical antipsychotic medications for any of these off-label indications, compared with placebo or active therapy. If atypical antipsychotic medications are going to be used for these indications, then trial evidence is necessary for clinicians, patients, and policymakers to predict the expected benefits.

More head-to-head trials are needed to compare atypical antipsychotics for conditions other than dementia. While the evidence we reviewed does not support the likelihood of major differences in efficacy between atypical antipsychotics, this hypothesis still needs rigorous testing.

Greater agreement is needed about which outcomes to report for most all of these conditions to facilitate easier comparisons across trials. Specifically, it would be useful to have agreement on the most important outcomes for each condition.

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Appendix A. Exact Search Strings

PsycInfo Searches
Searched: 1/7/05

Off-label & drug names – 6 citations
Off-label & conditions –- 41 citations
clinical trials & drug names & conditions –- 28 citations
clinical trials & drug names & conditions & off-label – 0 citations
drug names & conditions – 657 citations
off-label & drug names & conditions – 1 citation

Total Unique Results in PsycInfo: 702

Search Strategies:

Conditions
(((su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder")) or ((su: dementia OR su: depression)) or (kw: severe w geriatric w agitation OR kw: geriatric w agitation) and yr: 1990-2005) or (((kw: personality w disorders OR kw: obsessive w compulsive w disorder OR kw: obsessive w compulsive w personality w disorder OR kw: posttraumatic w stress w disorder OR kw: ptsd OR kw: ocd OR kw: post w traumatic w stress OR kw: obsessive w compulsive)) or ((kw: dementia OR kw: depression)) or (kw: severe w geriatric w agitation OR kw: geriatric w agitation) and yr: 1990-2005)
Total Results: 96355

Off-Label
kw: off w label or kw: off-label OR kw: offlabel OR kw: atypical w use OR kw: non w intended w use OR kw: non w intentional w use OR kw: "not" w intended w use and yr: 1990-2005
Total Results: 346

Clinical Trials
(de= "clinical trials") or ((kw: controlled w clinical w trial OR kw: controlled w clinical w trials OR kw: randomized w trial OR kw: randomized w trials OR kw: randomized w controlled w trial OR kw: randomized w controlled w trials OR kw: clinical w trial OR kw: clincal w trials)) and yr: 1990-2005
Total Results: 4709

Drug Names
(kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone) or ((de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone)) and yr: 1990-2005
Total Results: 3698

The Cochrane Central Register of Controlled Trials (CENTRAL) Searches
(Note: Clinical trial terms were not included in search strategy as this database is limited to controlled trials already)
Searched: 1/7/05

Off-label & drug names -- 0
Off-label & conditions -- 0
Drug names & conditions & off-label -- 0
Drug names & conditions -- 299

Total Unique Results in Cochrane CENTRAL: 299

Search Strategies:

Off-label
("atypical use" OR "off label" OR "non intended use" OR "non intentional use" OR "not intended use" OR "use not intended") in All Fields,
Limited to: 1990 to 2005
Total Results: 1

Drug names
(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) in Abstract or
(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) in Keywords or
(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) in Record Title or
(MeSH descriptor Risperidone explode all trees in MeSH products)
Limited to: 1990 to 2005
Total Results: 1901

Conditions
("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation) in Abstract or ("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation) in Record Title or ("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation) in Keywords
OR
(MeSH descriptor Personality Disorders explode all trees in MeSH products OR
MeSH descriptor Dementia explode all trees in MeSH products OR MeSH descriptor Depression explode all trees in MeSH products OR MeSH descriptor Depressive Disorder explode all trees in MeSH products OR MeSH descriptor Obsessive-Compulsive Disorder explode all trees in MeSH products ORMeSH descriptor Stress Disorders, Post-Traumatic explode all trees in MeSH products)
Limited to: 1990 to 2005
Total Results: 16389

Cochrane Database - Search Strategy
(Antipsychotic Agents[MeSh descriptor] OR risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) AND (depression OR dementia OR obsessive compulsive disorder OR post traumatic stress disorder OR ptsd OR off label OR off-label)
Date Searched: 12/15/2004
Limited search to: The Cochrane Database of Systematic Reviews
Total Results: 78

PubMed Search Strategy
("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone) AND (depression OR dementia OR obsessive compulsive disorder OR post traumatic stress disorder OR ptsd OR off label OR off-label)
Date Searched: 12/15/2004
Limited to: Systematic Reviews
Total Results: 95

PubMed Search Strategy

Limited: 1990-2005
Database searched: January 4, 2005
Total Results: 996

[(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) OR ("Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name] OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name])
AND
“atypical use” OR “off label” OR “non intended” OR “non intentional”
AND
("Personality Disorders"[MeSH] OR "Dementia"[MeSH] OR "Depression"[MeSH] OR "Depressive Disorder"[MeSH] OR "Obsessive-Compulsive Disorder"[MeSH] OR "Stress Disorders, Post-Traumatic"[MeSH]) OR ("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*” OR ptsd OR severe geriatric agitation OR geriatric agitation)]

OR

[(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) OR ("Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name] OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name])
AND
“atypical use” OR “off label” OR “non intended” OR “non intentional”]

OR

[“atypical use” OR “off label” OR “non intended” OR “non intentional”
AND
("Personality Disorders"[MeSH] OR "Dementia"[MeSH] OR "Depression"[MeSH] OR "Depressive Disorder"[MeSH] OR "Obsessive-Compulsive Disorder"[MeSH] OR "Stress Disorders, Post-Traumatic"[MeSH]) OR ("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*” OR ptsd OR severe geriatric agitation OR geriatric agitation)]

OR

[(Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone) OR ("Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name] OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name])
AND
("Personality Disorders"[MeSH] OR "Dementia"[MeSH] OR "Depression"[MeSH] OR "Depressive Disorder"[MeSH] OR "Obsessive-Compulsive Disorder"[MeSH] OR "Stress Disorders, Post-Traumatic"[MeSH]) OR ("Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*” OR ptsd OR severe geriatric agitation OR geriatric agitation)]

SCEPC Anti-psychotic Drug Review
Article Screener- Final

Reviewers: **Assigned on:**

Article ID

#Error

Citation: #Error

#Error

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

Aripiprazole..... ☐
Olanzapine ..... ☐
Quetiapine ..... ☐

Risperidone ..... ☐
Ziprasidone..... ☐
None of the above…… ☐ **(STOP)**

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

Dementia ..... ☐
Depression ..... ☐
Obsessive-compulsive disorder..... ☐

Personality disorders (DSM IV) ..... ☐
PTSD..... ☐
Severe geriatric agitation..... ☐

Insomnia..... ☐
Autism (including children 17 & under)..... ☐
Tourette's (including children 17 & under).... ☐

None of the above…… ☐(**STOP)**

3. Study population: **Circle one**

Human included..... 1
Only animal or cell lines ……..2**(STOP)**

4. Study design: **Circle one**

Descriptive (historical, editorial etc.) ..1**(STOP)**
Non-systematic review…… 2**(STOP)**
Systematic review / Meta-analysis…..3**(STOP)**

RCT *only* 4
CCT *only* 5
Trial + Open label extension..... 6
Case series / Case report..... 7
Cohort..... 8
Case control 9
Other 10

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

Yes 1
No..... 2

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

Enter # or 999 if no sample reported)

___ ___ ___ ___ ___

7. Does article report on the following: **Circle one**

Efficacy 1
Safety / Adverse events..... 2
Both 3
Neither ..... 4 **(STOP)**

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

___ ___ ___ ___ ___

Duration **Units**

Units

01. Hour	03. Week	05. Year
02. Day	04. Month	99. NR

9. Language of article: **Circle one**

English..... 1
Other..... 2

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

Yes..... 1
No 2
If YES, which one(s) :

_____
(Enter study ID #, author or 9999 if don't know.)

11. Is there a reference that needs to be checked? **Circle one**

Yes..... 1
No 2
If YES, which one(s) :

_____
(Enter reference # &/or author or 9999 if don't know.)

NOTES:

RAND SCEPC Anti-Psychotic Drugs Project
Detailed Abstraction Form

FINAL 06-20-05

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

Design: (CIRCLE ONE)
RCT 1
CCT 2
Trial + open label extension 3
Other design 4 (STOP)

Is the study described as randomized? (CIRCLE ONE)
Yes 1
No 2

If the study was randomized, was method of randomization appropriate? (CIRCLE ONE)
Yes 1
No 2
Method not described 8
Not applicable (not randomized) 9

Is the study described as: (CIRCLE ONE)
Double blind 1
Single blind, patient 2
Single blind, outcome assessment 3
Single blind, not described 4
Open 5
Blinding not described 8
Not applicable 9

If reported, was the method of double blinding appropriate? (CIRCLE ONE)
Yes 1
No 2
Double blinding method not described 8
Not applicable 9

If study was randomized, did the method of randomization provide for concealment of allocation? (CIRCLE ONE)
Yes 1
No 2
Concealment not described 8
Not applicable (not randomized) 9

Are withdrawals (W) and dropouts (D) described? (CIRCLE ONE)
Yes, reason described for **all** W and D 1
Yes, reason described for **some** W and D 2
Not described 8
Not applicable 9

What was the study's funding source? (CHECK ALL THAT APPLY)
Government ❑
Hospital ❑
Industry ❑
Private (non-industry) ❑
Other (code(s): _____) ❑
Unclear ❑
Not reported ❑

Last saved: 1/16/2007

RAND SCEPC Anti-Psychotic Drugs Project
Detailed Abstraction Form

In what country was the study conducted? (CHECK ALL THAT APPLY)

US ❑
Canada ❑
UK ❑

Western Europe ❑
Australia/New Zealand ❑
Other (enter code _____ , _____ , _____)❑
Not reported.....❑

What was the percent of male participants?
(ENTER NUMBER OR 999)

___ ___ ___ %

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

Caucasian..... ❑
African Ancestry..... ❑
Hispanic..... ❑

Asian/Pacific Islander ..... ❑
Native American ..... ❑
Eskimo/Inuit ..... ❑

Other-Not otherwise specified ..... ❑
Other (enter code): ..... ❑

_____ , _____ , _____ , _____
Not reported..... ❑

What was reported for the following questions regarding subjects ages? (Enter number 999 for not reported)

Mean Age..... _____
Median Age ..... _____
Age Range .... _____ to _____

What were the study's inclusion criteria?
(Enter code or 999 if NR)

Enter code: _____ , _____ , _____ , _____ ,
_____ , _____ , _____ , _____

What were the study's exclusion criteria?
(Enter code or 999 if NR)

Enter code: _____ , _____ , _____ , _____ ,
_____ , _____ , _____ , _____

What were the comorbidities reported in the study?
(Enter code or 999 if NR)

Enter code: _____ , _____ , _____ , _____ ,
_____ , _____ , _____ , _____

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CHARACTERISTICS OF THE CONDITIONS:

Which of the following patient characteristics are described for the following conditions? Please check the appropriate boxes. For each condition please note the criteria that was used to establish the primary diagnosis and the method by which the primary diagnosis was establish. Use codes in box below for criteria & method.

Criteria	Method
1. DSM-IV	1. Clinician established
2. DSM-III-R	2. Structured interview
3. Not reported	3. Not reported
4. Not applicable	4. Not applicable

Depression: Criteria: _____ Method: _____

- Mood disorder (depression or bipolar) without psychotic features ❑
- Mood disorder (depression or bipolar) with psychotic features ❑
- Psychosis with depression ❑
- Psychosis without depression ❑
- Other depression (specify: _____) ❑

Personality Disorder: Criteria: _____ Method: _____

- Paranoid ❑
- Schizoid ❑
- Schizotypal ❑
- Antisocial ❑
- Borderline ❑
- Histrionic ❑
- Narcissistic ❑
- Avoidant ❑
- Dependent ❑
- Obsessive-compulsive ❑
- Personality disorder not otherwise specified ❑
- Other personality disorder (specify _____) ❑

Dementia: Criteria: _____ Method: _____

- Alzheimer's type ❑
- Vascular Dementia ❑
- With behavioral disturbance ❑
- Without behavioral disturbance ❑
- Dementia not otherwise specified ❑
- Other Dementia (specify _____) ❑

OCD: Criteria: _____ Method: _____

- Obsessive compulsive disorder ❑

PTSD: Criteria: _____ Method: _____

- Civilian ❑
- Military ❑
- Other PTSD (specify _____) ❑

Severe Geriatric Agitation: Criteria: _____ Method: _____

- Delirium ❑
- Dementia with agitation ❑
- Other severe geriatric agitation (specify _____) ❑

Insomnia: Criteria: _____ Method: _____

- Insomnia ❑

Autism: Criteria: _____ Method: _____

- Autism ❑

Tourette's: Criteria: _____ Method: _____

- Tourette's syndrome ❑

Primary condition(s) not listed above with outcomes of interest ❑

Enter code: _____ , _____ , _____ , _____ , _____

RAND SCEPC Anti-Psychotic Drugs Project
Detailed Abstraction Form

INTERVENTIONS

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

Arm/ Group	Sample size	Intervention	Dose	Units	Frequency	Dose Description	Duration of treatment	Units	Co-intervention(s)
1	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
2	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
3	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
4	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported.	Enter code(s): 1.Placebo 2.Control ETC…	Enter # or range 998. Not applicable 999. Not reported	Enter a number 1. g 2. mg 3. 4. 9.NR	Enter a number 1. Hour 2. Day 3. Week 4. Month 5. Year 9. NR	Enter a number 1.Fixed single dose 2.Fixed titration schedule 3.Flexible dose 4.Average final dose 9.NR	Enter a number 997. Variable 998. NA 999. NR	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.NA 9. NR	Enter code(s) or 998. Not applicable 999. Not reported

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Interventions (continued)

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

Arm/ Group	Sample size	Intervention	Dose	Units	Frequency	Dose Description	Duration of treatment	Units	Co-intervention(s)
5	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
6	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
7	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
8	_____ N ENTERING _____ N COMPLETING	_____	_____	_____	_____	_____	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported.	Enter code(s): 1.Placebo 2.Control ETC…	Enter # or range 998. Not applicable 999. Not reported	Enter a number 1. g 2. mg 3. 4. 9.NR	Enter a number 1. Hour 2. Day 3. Week 4. Month 5. Year 9. NR	Enter a number 1.Fixed single dose 2.Fixed titration schedule 3.Flexible dose 4.Average final dose 9.NR	Enter a number 997. Variable 998. NA 999. NR	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.NA 9. NR	Enter code(s) or 998. Not applicable 999. Not reported

18. OUTCOMES: Please enter the outcomes measured and the final followup time for each outcome measured.

Outcome code	Final Followup	
Outcome code	Number	Unit

Units:

1. Hour
2. Day
3. Week
4. Month
5. Year
9. NR

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Observational Data Abstraction Form

Article ID:_____ Reviewer: Walter Mojica

Study Number: ___of____

Evidence Table

1. What is the study trial name?

   Enter code or 999 for no name:_____

2. Is the study design trial with crossover? (CIRCLE ONE)

   Yes 1
   No 2

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

   Multi-center ..... ❑
   Single setting ..... ❑
   Community practice ..... ❑
   Other (enter code: _____, _____, _____, _____)... ❑

   [ ] Setting not reported..... ❑

4. Run-in period table: (Enter 999 in first column if no run-in.)

Length	Units	Placebo/Medication	How used for randomization?

5. Wash-out period table: (Enter 999 in first column if no wash-out.)

Length	Units	Placebo/Medication	How used for randomization?

6. Time of assessment: When were outcomes measured? (CIRCLE ONE)

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

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

Units for Q4, Q5, Q6

1. Hour	5. Year
2. Day	8. ND
3. Week	9. NA
4. Month	997. Variable
	999. NR

7. Sample size: (Enter N or 999 for not reported)

   Screened: _____ Eligible: _____

   Withdrawn: _____ Loss to follow-up: _____

8. What was the method of adverse events assessment?

(CHECK ALL THAT APPLY)

Monitored ..... ❑
Elicited by investigator ..... ❑
Reported spontaneously by patient ..... ❑
Other (enter code: _____, _____, _____, _____)... ❑
Not reported ..... ❑

Quality Assessment

9. Were outcome assessors masked to the treatment allocation?

(CIRCLE ONE)

Yes 1
Yes, but not described 2
No 3
Not reported 9

10. Was the care provider masked to the treatment allocation?

(CIRCLE ONE)

Yes 1
Yes, but not described 2
No 3
Not reported 9

11. Was the patient masked to the treatment allocation?

(CIRCLE ONE)

Yes 1
Yes, but not described 2
No 3
Not reported 9

12. Did the article report the following? (CHECK ALL THAT APPLY)

	Yes	No
Attrition	❑	❑
Crossovers	❑	❑
Adherence	❑	❑
Contamination	❑	❑

13. Did the study include an intention-to-treat analysis, or provide the data needed to calculate it?

(CIRCLE ONE)

Yes 1
No 2

14. Were there post-randomization exclusions, any differences between groups at follow-ups?

(CIRCLE ONE)

Yes (Enter numbers in table below) 1
No 2
Unable to determine 3

Arm	# Exclusions	Arm	# Exclusions
1		5	
2		6	
3		7	
4		8	

15. Were patients class-naive?

(CIRCLE ONE)

Yes 1
No 2
Not reported 9
(If NO, enter code(s): _____, _____, _____, _____,
_____, _____, _____, _____)

16. Any authors from drug companies funding the study? (CIRCLE ONE)

Yes 1
No 2
Unclear 3
Not reported 9

17. Did the article include a statement on the role of the funder?

(CIRCLE ONE)

Yes 1
No 2

RAND SCEPC Anti-Psychotic Drugs Project
Observational Data Abstraction Form

Article ID:_____ Reviewer:_____

First Author: _____Year: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. In what country was the study conducted? **(CHECK ALL THAT APPLY)**
   - US ..... ❑
   - Canada ..... ❑
   - UK ..... ❑
   - Western Europe ..... ❑
   - Australia/New Zealand ..... ❑
   - Other (enter text: _____) .... ❑
   - Not reported ..... ❑

2. What was the percent of male participants?
   (ENTER NUMBER OR NR)
   ___ ___ ___ %

3. What was reported for the following questions regarding subjects ages? (Enter NR for not reported)
   - Mean Age ..... _____
   - Median Age ..... _____
   - Age Range ..... _____ to _____

4. Sample size: (Enter NR for not reported)
   - Screened: _____ Eligible: _____
   - Withdrawn: _____ Loss to follow-up: _____

5. What was the racial/ethnic population studied?
   (Check all that apply)
   - Caucasian ..... ❑
   - African Ancestry ..... ❑
   - Hispanic ..... ❑
   - Asian/Pacific Islander ..... ❑
   - Native American ..... ❑
   - Eskimo/Inuit ..... ❑
   - Other-Not otherwise specified ..... ❑
   - Other (enter text): ..... ❑
     _____
   - Not reported ..... ❑

6. What were the study's inclusion criteria?
   Enter text or NR for not reported:
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____

7. What were the study's exclusion criteria?
   Enter text or NR for not reported:
   _____
   _____
   _____
   _____
   _____
   _____

RAND SCEPC Anti-Psychotic Drugs Project
Observational Data Abstraction Form

_____
_____

INTERVENTIONS

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

Arm/ Group	Sample size	Intervention	Dose	Units	Frequency	Dose Description	Co-intervention(s)
1	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____	_____	____	____	_____	_____ _____ _____ _____ _____ _____
2	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____	_____	____	____	_____	_____ _____ _____ _____ _____ _____
3	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____	_____	____	____	_____	_____ _____ _____ _____ _____ _____
4	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____	_____	____	____	_____	_____ _____ _____ _____ _____ _____

RAND SCEPC Anti-Psychotic Drugs Project
Observational Data Abstraction Form

9. When, relative to the start of the intervention or exposure, Were outcomes reported?

(Enter the number/text in the appropriate box)

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
7th follow-up		
8th follow-up		
9th follow-up		
10th follow-up		
11th follow-up		
12th follow-up		
13th follow-up		
14th follow-up		
15th follow-up		
16th follow-up		
17th follow-up		
18th follow-up		
19th follow-up		
20th follow-up		
21st follow-up		
22nd follow-up		
23rd follow-up		
24th follow-up		

C1: Evidence Tables – Head to Head Trials

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**
Dementia and Agitation Olanzapine & Risperidone (Fontaine CS et al., 2003) US	Design: RCT Setting: Long-term care Jadad: 3	Inclusion criteria: Medically stable, Able to comply with oral, non-liquid medication, CGI >= 4, ADCS >= 25 Exclusion criteria: Neuroleptic malignant syndrome, Atypical antipsychotics sensitivity, Major depressive disorder, Schizophrenia, Bipolar disorder, Some antihypertensive drugs, Some antibiotics, Antiparkinsonian drug treatment	Olanzapine-6.65 mg/day average final dose Risperidone-1.47 mg/day average final dose Duration: 0.5 month	None 3 dy of Psychotropics for randomization not described
Dementia and Agitation Olanzapine & Risperidone (Herz LR et al., 2002) US	Design: RCT Setting: Veterans Jadad: 3	Inclusion criteria: Age > 65 Exclusion criteria: NR	Placebo-dosage not reported Risperidone-0.5-4 mg/day flexible dose Olanzapine-2.5-20 mg/day flexible dose Duration: 1.5 months	None None
Dementia and Depression Quetiapine & Risperidone (Mullen J et al., 2001) US	Design: RCT Setting: Multi-center Jadad: 1	Inclusion criteria: Age >= 18 Exclusion criteria: Lactating, Medically significant disorders, Clozapine treatment, Clozapine unresponsiveness, Previous drug-induced agranulocytosis, Pregnant, Participation in previous quetiapine trial, Participation in previous clinical trial within 4 months, Risperidone treatment within 4 months	Quetiapine mean dose 253.9 mg/day Risperidone mean dose 4.4 mg/day Duration: 4.0 months	None None

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**
Dementia, Depression and Agitation Olanzapine & Risperidone (Deberdt WG et al., 2005) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age >= 40, NPI or NPI/NH >= 6 sum of hallucinations and delusional items, Assisted Living Facility resident or Nursing home resident Exclusion criteria: Frontotemporal dementia, Lewy body dementia, MMSE > 24, Parkinsons disease, Picks disease	Placebo Olanzapine-5.2 mg mean daily dose Risperidone-1.0 mg mean daily dose Duration: 2.5 months	None 3-14 dy of Placebo for patients who completed the wash-out period
Depression Olanzapine & Risperidone (Levitt A et al., 2004) Canada	Design: RCT Setting: Outpatient Jadad: 3	Inclusion criteria: Treatment-resistant depression, Failed SSRI, 18-65 years, ≥16 on HAM-D, SNRI for at least 4 weeks Exclusion criteria: Suicidal, current Axis 1 DSM IV diagnosis other than anxiety disorder, substance abuse in past 3 months, pregnant, lactating or certain other medications	SRIs or Velanfaxine + Risperidone-mean dose 1.6±0.9 mg/day SRIs or Velanfaxine + Olanzapine-mean dose 9.0±4.6 mg/day Duration: 1.5 months	None None
Dementia Olanzapine & Risperidone (Mulsant BH et al., 2004) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age > 65, 1 year duration primary condition, MMSE score of 7-26 and NPI frequency times severity score of ≥4 on delusions, hallucinations or both Exclusion criteria: Psychosis before dementia onset, Delirium, Inability to swallow oral medication or unable to cooperate with study	Risperidone-0.76 mg/day average final dose Olanzapine-5.22 mg/day average final dose Duration: 1.5 months	7 dy of Placebo for randomization not described 3 dy of ND for randomization not described

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**
Depression Olanzapine & Risperidone (Tollefson GD et al., 1999) Belgium France Switzerland Netherlands South Africa Germany Spain UK US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Schizophrenia, schizophreniform disorder or schizoaffective disorder, ≥18 years old Exclusion criteria: Comorbid or major axis1 disorder, pregnant or lactating, Failure to show at least minimal clinical response with at least 3 antipsychotics in 3 classes	Olanzapine-17.2 mg/day mean modal dose Risperidone-7.2 mg/day mean modal dose Duration: 7.0 months	None 2-9 days for oral antipsychotic and at least one injection cycle for depot antipsychotics
Depression Olanzapine & Ziprasidone (Kinon BJ et al., 2005) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: MADRS >= 16, MADRS >= 4 on Item 2 Exclusion criteria: Previous sensitivity or unresponsiveness to stuffy drug	Olanzapine-10 mg/day fixed single dose Olanzapine-15 mg/day fixed single dose Olanzapine-20 mg/day fixed single dose Ziprasidone-80 mg/day fixed single dose Ziprasidone-120 mg/day fixed single dose Ziprasidone-160 mg/day fixed single dose Duration: 24.0 months	None None

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**
Depression Olanzapine & Ziprasidone (Simpson GM et al., 2004) US	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: CGI >= 4, PANSS with score >= 4 on at least 1 items on positive symptoms subscale Exclusion criteria: Pregnant, Hospitalized >= 2 wks, Abnormal laboratory results, DSM-IV Axis I disorder, not including primary condition studied, Depot neuroleptic within 1 treatment cycle, Resistant to antipsychotic treatment, Suicidal or violent, Olanzapine > 14 days life time exposure or olanzapine daily dose >10 m	Ziprasidone-139.0 mg/day average final dose Olanzapine-13.0 mg/day average final dose Duration: 1.5 months	None 1-3 wk of Antipsychotics for randomization not described

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**	**Withdrawn/ Lost to FU/ Analyzed**
Dementia and Agitation Olanzapine & Risperidone (Fontaine CS et al., 2003) US	Lorazepam	Assessed at baseline and 15 day: CGI, NPI, E-BEHAVE-AD, PGDRS, MOSES, QUALID, MMSE .	83/NR 33% male Caucasian, NOS	NR/47/39	4/0/35
Dementia and Agitation Olanzapine & Risperidone (Herz LR et al., 2002) US	NR	Assessed at baseline and 6 weeks: BPRS, CMPNB	NR/NR 100% male NR	NR/29/29	1/0/28
Dementia and Depression Quetiapine & Risperidone (Mullen J et al., 2001) US	Anticholinergic medications, Antidepressants , Antipsychotics (except olanzapine, sertindole, clozapine), Mood stabilizers, Rescue Medications (haloperidol, benzodiazepines, anti-EPS)	Assessed at baseline and 16 weeks: HAM_D_HDRS, CGI, PANSS	45/18-87 51% male Caucasian, African-American, Hispanic, Asian, Other	NR/728/ 728	235/NR/NR
Dementia, Depression and Agitation Olanzapine & Risperidone (Deberdt WG et al., 2005) US	Anticholinergics , Benzodiazepines permitted	Assessed at baseline and 10 weeks: NPI, CGI, NPI-NH, CMAI, BPRS, CSDD, PDS, MMSE	79/NR 34% male Caucasian, African-American, NOS	NR/494/ 494	NR/NR/493

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**	**Withdrawn/ Lost to FU/ Analyzed**
Depression Olanzapine & Risperidone (Levitt A et al., 2004) Canada	NR	Assessed at baseline and 6 weeks: HAM_D_HDRS, MADRS, HAM-A, CGI-I	47.4±11.7 RIS; 43.2±9.2 OLA 46% male RIS; 36% male OLA NR	NR/43/43	NR/NR/43
Dementia Olanzapine & Risperidone (Mulsant BH et al., 2004) US	Lorazepam, Benzodiazapine, Cholinesterase inhibitors	Assessed at baseline and 6 weeks: NPI, CGI	84/68-95 23% male Caucasian, African-American, Hispanic	NR/86/86	NR/NR/85
Depression Olanzapine & Risperidone (Tollefson GD et al., 1999) Belgium France Switzerland Netherlands South Africa Germany Spain UK US	Anticholinergic medications	Assessed at baseline and 28 weeks: PANSS, PDC, CGI	36/18-65 65% male Caucasian, NOS	NR/339/339	NR/NR/254
Depression Olanzapine & Ziprasidone (Kinon BJ et al., 2005) US	NR	Assessed at baseline and 24 weeks: MADRS, GAF, CDSS	42/NR 63% male Caucasian, NOS	NR/394/NR	NR/NR/NR
Depression Olanzapine & Ziprasidone (Simpson GM et al., 2004) US	Anti-EPS medications, Lorazepam	Assessed at baseline and 6 weeks: BPRS, PANSS, CGI, CDSS	38/8-59 65% male Caucasian, African-American, Hispanic, Asian, NOS	367/269/ 269	NR/NR/269

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia and Agitation Olanzapine & Risperidone (Fontaine CS et al., 2003) US	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored	Olanzapine vs Risperidone: Asystole: 5.0%(1/20) vs 0.0%(0/19) Brain stem stroke: 5.0%(1/20) vs 0.0%(0/19) Diaphoresis, fainting, & asystole: 5.0%(1/20) vs 0.0%(0/19) Drowsiness: 0.0%(0/20) vs 21.1%(4/19) Dystonia: 0.0%(0/20) vs 5.3%(1/19) Falls: 30.0%(6/20) vs 21.1%(4/19) Mild EPS: 0.0%(0/20) vs 10.5%(2/19) Rash w/elevated BP, pulse, white blood cell count, & temperature: 5.0%(1/20) vs 0.0%(0/19) Unsteady gait, falls: 10.0%(2/20) vs 0.0%(0/19)	Olanzapine vs Risperidone: Withdrawals: 20.0%(4/20) vs 10.5%(2/19) Withdrawals due to adverse events: 20.0%(4/20) vs 0.0%(0/19)
Dementia and Agitation Olanzapine & Risperidone (Herz LR et al., 2002) US	Insufficient statistics for effect-size calculation.	NR	No adverse events reported.	Placebo vs Risperidone vs Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia and Depression Quetiapine & Risperidone (Mullen J et al., 2001) US	Depression_mood-Change in HAM-D at 16 weeks: Quetiapine vs Risperidone-SMD = 0.174(-0.009,0.357)	Monitored	Quetiapine vs Risperidone: At least one adverse event: 72.3%(400/553) vs 61.1%(107/175) Agitation: 6.1%(34/553) vs 1.7%(3/175) Death: 0.7%(4/553) vs 0.0%(0/175) Dizziness: 12.7%(70/553) vs 6.9%(12/175) Dry mouth: 14.5%(80/553) vs 6.9%(12/175) EPS: 29.8%(161/541) vs 40.9%(70/171) Headache: 9.4%(52/553) vs 6.3%(11/175) Insomnia: 11.8%(65/553) vs 9.7%(17/175) Somnolence: 31.3%(173/553) vs 15.4%(27/175) Weight gain: 2.5%(14/553) vs 3.4%(6/175) Weight loss: 0.7%(4/553) vs 0.0%(0/175)	Quetiapine vs Risperidone: Withdrawals: 31.8%(175.854/553) vs 33.7%(58.975/175) Withdrawals due to adverse events: 8.7%(48.111/553) vs 5.1%(8.925/175)

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia, Depression and Agitation Olanzapine & Risperidone (Deberdt WG et al., 2005) US	Dementia_agitation-Change in CMAI-aggression at 10 weeks: Placebo vs Olanzapine-SMD = 0.106(-0.145,0.356) Dementia_agitation-Change in CMAI-aggression at 10 weeks: Placebo vs Risperidone-SMD = -0.021(-0.272,0.23) Dementia_agitation-Change in CMAI-aggression at 10 weeks: Olanzapine vs Risperidone-SMD = -0.127(-0.328,0.074) Dementia_global-Change in NPI-NH total at 10 weeks: Placebo vs Olanzapine-SMD = 0.095(-0.155,0.344) Dementia_global-Change in NPI-NH total at 10 weeks: Placebo vs Risperidone-SMD = 0.016(-0.234,0.266) Dementia_global-Change in NPI-NH total at 10 weeks: Olanzapine vs Risperidone-SMD = -0.079(-0.279,0.122) Dementia_psychosis-Change in NPI-NH Psychosis at 10 weeks: Placebo vs Olanzapine-SMD = 0.201(-0.049,0.45) Dementia_psychosis-Change in NPI-NH Psychosis at 10 weeks: Placebo vs Risperidone-SMD = 0.12(-0.13,0.37) Dementia_psychosis-Change in NPI-NH Psychosis at 10 weeks: Olanzapine vs Risperidone-SMD = -0.08(-0.281,0.12) Dementia_severity-Change in CGI-S at 10 weeks: Placebo vs Olanzapine-WMD = 0(-0.186,0.186) Dementia_severity-Change in CGI-S at 10 weeks: Placebo vs Risperidone-WMD = 0(-0.186,0.186) Dementia_severity-Change in CGI-S at 10 weeks: Olanzapine vs Risperidone-WMD = 0(-0.148,0.148)	Monitored, reported by patient	placebo vs olanzapine vs risperidone: Abnormal gait: 3.2%(3/94) vs 9.9%(20/203) vs 10.7%(21/196) Accidental injury: 10.6%(10/94) vs 13.3%(27/203) vs 8.2%(16/196) Agitation: 13.8%(13/94) vs 18.2%(37/203) vs 15.3%(30/196) Anorexia: 8.5%(8/94) vs 6.4%(13/203) vs 5.6%(11/196) Asthenia: 2.1%(2/94) vs 7.4%(15/203) vs 8.7%(17/196) Confusion: 6.4%(6/94) vs 14.3%(29/203) vs 10.2%(20/196) Delusions: 5.3%(5/94) vs 9.4%(19/203) vs 7.7%(15/196) Dizziness: 4.3%(4/94) vs 6.4%(13/204) vs 5.6%(11/196) Dyspnea: 3.2%(3/94) vs 0.0%(0/203) vs 3.1%(6/196) Flu symptom: 3.2%(3/94) vs 1.0%(2/203) vs 0.0%(0/196) Hallucinations: 5.3%(5/94) vs 12.8%(26/203) vs 8.7%(17/196) Hostility: 1.1%(1/94) vs 6.9%(14/203) vs 6.6%(13/196) Insomnia: 5.3%(5/94) vs 6.9%(14/203) vs 5.6%(11/196) Nervousness: 9.6%(9/94) vs 7.9%(16/203) vs 10.2%(20/196) Peripheral edema: 1.1%(1/94) vs 5.4%(11/203) vs 6.1%(12/196) Somnolence: 8.5%(8/94) vs 23.2%(47/203) vs 18.9%(37/196) Urinary incontinence: 1.1%(1/94) vs 9.4%(19/203) vs 12.8%(25/196) Weight gain: 1.1%(1/94) vs 5.4%(11/203) vs 3.1%(6/196) Weight change in kg: Placebo-90 people (-0.1 kg mean, SD) vs Olanzapine-194 people (1.0 kg mean, SD) vs Risperidone-190 people (0.1 kg mean, SD)	placebo vs olanzapine vs risperidone: Withdrawals: 20.2%(18.988/94) vs 37.7%(76.908/204) vs 31.1%(60.956/196) Withdrawals due to adverse events: 3.2%(3.008/94) vs 16.2%(33.048/204) vs 8.7%(17.052/196)

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine & Risperidone (Levitt A et al., 2004) Canada	Insufficient statistics for effect-size calculation.	Monitored	No adverse events reported. Weight change in kg: Risperidone-21 people (0.4 kg mean, SD NR) vs Olanzapine-22 people (3.6 kg mean, SD NR)	Risperidone + (SRI or venlafaxine) vs Olanzapine + (SRI or venlafaxine): Withdrawals: Not reported Withdrawals due to adverse events: Not reported
Depression Olanzapine & Risperidone (Mulsant BH et al., 2004) US	Insufficient statistics for effect-size calculation.	Monitored	Risperidone vs Olanzapine: Somnolence: 2.8%(2/71) vs 7.1%(6/84) UKU-based anticholinergic events: 16.9%(12/71) vs 14.3%(12/84)	Risperidone vs Olanzapine: Withdrawals: 17 (19.8%) Withdrawals due to adverse events: 5.6%(4/71) vs 2.4%(2/84)

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine & Risperidone (Tollefson GD et al., 1999) US	Depression_mood-Change in PDC at 8 weeks: Olanzapine vs Risperidone-SMD = 0.254(0.007,0.501)	Monitored	Olanzapine vs Risperidone: Backache: 6.6%(11/167) vs 13.3%(22/165) Blurred vision: 9.6%(16/167) vs 20.6%(34/165) Breathing difficulties: 7.2%(12/167) vs 14.5%(24/165) Delayed ejaculation: 1.8%(3/167) vs 7.3%(12/165) Early waking: 12.0%(20/167) vs 24.2%(40/165) Increased dreams/nightmares: 11.4%(19/167) vs 19.4%(32/165) Dystonic events: 1.7%(3/167) vs 6.0%(10/165) Parkinsonian events: 9.9%(17/167) vs 18.6%(31/165) Pseudoparkinsonism as per Simpson-Angus rating scale: 12.5%(21/167) vs 22.3%(37/165) EPS: 18.6%(31/167) vs 31.1%(51/165) Akathisia (spontaneously reported): 9.9%(17/167) vs 10.8%(18/165) Akathisia as per Barnes Akathisia Scale: 15.9%(27/167) vs 27.3%(37/165) Dyskinetic events (spontaneously reported): 2.3%(4/167) vs 3.0%(5/165) Dyskinetic symptoms at last visit as per categorical analysis of AIMS & diagnositc criteria of Schooler & Kane: 4.6%(7/167) vs 10.7%(45/165) Residual events: 1.7%(3/167) vs 0.6%(1/165) High prolactin concentration at any time: 51.2%(86/167) vs 94.4%(156/165) Low neutrophil concentrations at any time: 4.3%(7/167) vs 0.6%(1/165) Hypersalivation: 6.4%(7/167) vs 16.3%(17/165) Palpitations: 5.5%(6/167) vs 14.4%(15/165) Weight change in kg: Olanzapine – 167 people (mean 4.1, SD 5.9) vs Risperidone – 165 people (mean 2.3, SD 4.8)	Olanzapine vs Risperidone: Withdrawals: 42.4%(73/172) vs 52.7%(88/167) Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine & Ziprasidone (Kinon BJ et al., 2005) US	Depression_mood-Change in MADRS at 24 weeks: Olanzapine vs Ziprasidone-SMD = 1.032(0.822,1.243)	Monitored	Olanzapine vs Ziprasidone: Appetite decrease: 1.0%(2.02/202) vs 5.3%(10.176/192) Appetite increase: 10.4%(21.008/202) vs 4.2%(8.064/192) Bruxism: 0.0%(0/202) vs 2.1%(4.032/192) Dry mouth: 15.8%(31.916/202) vs 10.6%(20.352/192) Headache: 15.8%(31.916/202) vs 10.6%(20.352/192) Influenza: 0.0%(0/202) vs 2.6%(4.992/192) Insomnia: 12.4%(25.048/202) vs 18.0%(34.56/192) Irritability: 1.0%(2.02/202) vs 3.7%(7.104/192) Migraine NOS: 0.0%(0/202) vs 2.6%(4.992/192) Muscle twitching: 2.5%(5.05/202) vs 0.0%(0/192) Nausea: 7.9%(15.958/202) vs 11.1%(21.312/192) Peripheral edema: 3.0%(6.06/202) vs 0.0%(0/192) Psychosis NOS: 2.5%(5.05/202) vs 7.9%(15.168/192) Weight increased: 20.3%(41.006/202) vs 5.8%(11.136/192) Weight change in kg: Olanzapine-202 people (2.53 mean,4.91 SD) vs Ziprasidone-192 people (-1.65 mean,4.16 SD)	Olanzapine vs Ziprasidone: Withdrawals: 55.4% (111.908/202) vs 70.3% (134.976/192) Withdrawals due to adverse events: 16.0%(32.32/202) vs 26.0%(49.92/192)

Condition, Drug Author, Year Country, Trial named	Results	Method of adverse events assessment	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine & Ziprasidone (Simpson GM et al., 2004) US	Depression_severity-Change in CGI-S at 6 weeks: Olanzapine vs Ziprasidone-WMD = -0.05(-0.256,0.156)	Monitored, reported by patient, clinical observation	Ziprasidone vs Olanzapine: At least one adverse event: 84.6%(115/136) vs 71.4%(95/133) Body as a whole: 38.2%(52/136) vs 29.3%(39/133) Cardiovascular: 5.1%(7/136) vs 7.5%(10/133) Digestive: 40.4%(55/136) vs 30.8%(41/133) Endocrine: 0.7%(1/136) vs 0.0%(0/133) Hematic & lymphatic: 2.2%(3/136) vs 3.8%(5/133) Metabolic & nutritional: 3.7%(5/136) vs 10.5%(14/133) Musculoskeletal: 5.9%(8/136) vs 6.0%(8/133) Nervous: 60.3%(82/136) vs 48.1%(64/133) Respiratory: 17.6%(24/136) vs 12.0%(16/133) Skin & appendages: 10.3%(14/136) vs 7.5%(10/133) Special senses: 5.9%(8/136) vs 4.5%(6/133) Urogenital: 6.6%(9/136) vs 3.8%(5/133) Weight change in kg: Ziprasidone-136 people (0.9 mean, SD NR) vs Olanzapine-133 people (3.57 mean, SD NR)	Ziprasidone vs Olanzapine: Withdrawals: 48.5%(66/136) vs 36.8%(49/133) Withdrawals due to adverse events: 7.3%(10/136) vs 3.0%(4/133)

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
ADL	Activities of Daily Life
AIAQ	Anger, Irritability, and Assault Questionnaire
ASI	Addiction Severity Index
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Index
BDHI	Buss-Durkee Hostility Index
BDI	Beck Depression Index
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelsen Melancholia Scale
CAPS	Clinician Administered PTSD Scale
CDSS	Calgary Depression Scale for Schizophrenia
CES-D	Center for Epidemiologic Studies Depression Scale
CGI	Clinical Global Impression Scale
CMAI	Cohen-Mansfield Agitation Inventory
CM-PNB	Cohen-Mansfield Physically Non-Aggressive Behavior
CPRS	Children's Psychiatric Rating Scale
CSDD	Cornell Scale for Depression in Dementia
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DCM	Dementia Care Mapping
DES	Dissociative Experiences Scale
DTS	Davidson Trauma Scale
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
FAST	Functional Assessment Staging Rating Scale
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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C2: Evidence Tables – Active Control Trials

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Autism Olanzapine (Malone RP et al., 2001) US	Design: RCT Setting: NR Jadad: 3	Inclusion criteria: Age 5-17, CPRS = moderate impairment ≥ any 2 items Exclusion criteria: Medically significant disorders, Seizure disorder or epilepsy or risk, Neurological disorder, Psychotropic medications, Previous exposure to study drug	Haloperidol-1.4 mg/day average final dose Olanzapine-7.9 mg/day average final dose Duration: 1.5 months
Dementia and Agitation Olanzapine (Meehan KM et al., 2002) US, Russia	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Hospitalized/institutionalized, Nursing home resident, Age ≥ 55, PANSS ≥ 14 on the Excited Component and at least one individual PANSS ≥ 4 item score on scale 1-7, Clinically significant agitation, Exclusion criteria: Anticholinergic medications, Antipsychotic medications, Benzodiazepines, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, Abnormal laboratory results, Suicidal or violent,	Placebo-dosage not reported Lorazepam 1.0 mg/day Olanzapine-2.5-6.25 mg/day flexible dose Olanzapine-5.0-12.5 mg/day flexible dose Duration: 24 hours
Dementia and Agitation Quetiapine (Ballard C et al., 2005) UK	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: CMAI ≥ 39, Age ≥ 60, NPI = 4 Exclusion criteria: Antipsychotics treatment ≥ 4 wks, Cholinesterase treatment ≥ 4 wks, Previous sensitivity or unresponsiveness to stuffy drug, Severe internal or neurological disease, Medically significant disorders,	Placebo-dosage not reported Rivastigmine- min 9 mg/day Quetiapine-100 mg/day average final dose Duration: 6.5 months
Dementia and Agitation Risperidone (Chan WC et al., 2001) China	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 55, CMAI of at least 4 in one item and at least 3 in another, BEHAVE-AD ≥ 8 Exclusion criteria: Lewy body dementia, Neurological or medical conditions diminishing cognitive function, Psychosis/psychotic features, Medically significant disorders, Abnormal laboratory results, Allergic or toxic reactions to psychotropic medications, Neuroleptic malignant syndrome	Haloperidol-.90 mg/day average final dose Risperidone-.85 mg/day average final dose Duration: 3.0 months

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Dementia and Agitation Risperidone (De Deyn PP et al., 1999) Canada, UK, Europe	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age ≥ 55, Hospitalized/institutionalized, FAST ≥ 4, MMSE ≤ 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD ≥ 8 Exclusion criteria: Neurological or medical conditions diminishing cognitive function, Other psychiatric disorders, Severe internal or neurological disease, Abnormal laboratory results, Depot neuroleptic within 1 treatment cycle, Allergic or toxic reactions to psychotropic medication, Participation in a clinical trial with investigational drugs during the 4 weeks preceding trial	Placebo-dosage not reported Haloperidol-1.2 mg/day average final dose Risperidone-1.1 mg/day average final dose Duration: 3.0 months
Dementia and Agitation Risperidone (Suh GH et al., 2004) Korea	Design: RCT, Crossover Setting: Single center Jadad: 4	Inclusion criteria: Age ≥ 65, FAST ≥ 4, BEHAVE-D ≥ 8, CMAI ≥ 3 on any 2 items Exclusion criteria: Neurological or medical conditions diminishing cognitive function, Psychotic disorder, Severe internal or neurological disease, Medically significant disorders, Abnormal laboratory results, Allergic or toxic reactions to antipsychotic medications, Neuroleptic malignant syndrome,	Haloperidol-0.83 mg/day average final dose Risperidone-0.80 mg/day average final dose Duration: 2.0 months
Depression Olanzapine (David S JBAKWP, 2002) NR	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: NR Exclusion criteria: NR	Placebo-dosage not reported Lorazepam-1.0-3.0 mg/day flexible dose Lorazepam l-2.0-6.0 mg/day flexible dose IM Haloperidal 7.5 mg/d IM Olanzapine 2.5-10.0 mg/d Duration: 24 hours
Depression Olanzapine (McEvoy J et al.,) US, Canada, UK, Europe HGDH Study	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age 16-40, Psychotic symptoms before age 35, Psychotic symptoms for at least 1 mth, but not > 60 mth, PANSS with score ≥ 4 on at least 2 items on positive symptoms subscale, PANSS ≥ 5 in 1 psychotic item, CGI ≥ 4, Psychosis/psychotic features, Exclusion criteria: Pregnant, Clozapine treatment, Antipsychotic treatment > 16 wks in a lifetime, Lactating, Medically significant disorders, Previous sensitivity or unresponsiveness to stuffy drug, Alcohol or substance abuse or dependency, Suicidal or violent	Haloperidol-4.8 mg/day average final dose Olanzapine-10.2 mg/day average final dose Duration: 26.0 months

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Depression Olanzapine (Shelton RC et al., 2001)[1] (Tohen M et al., 1999) US	Design: Trial + open label Setting: NR Jadad: 2	Inclusion criteria: Resistant to antidepressant therapy, HAM-D ≥ 20 Exclusion criteria: Psychosis/psychotic features, Dysthymic disorder, Bipolar disorder	Fluoxetine- 52 mg/day average final dose Olanzapine-12.5 mg/day average final dose Olanzapine-13.5 mg/day average final dose, Fluoxetine-52 mg/day average final dose Duration: 4.0 months
Depression Olanzapine (Street JS et al., 2000)[1] (Street JS et al., 2000)[1] (Satterlee WG et al., 1995) NR	Design: RCT Setting: NR Jadad: 1	Inclusion criteria: Alzheimers, Psychosis/psychotic features Exclusion criteria: NR	Placebo Olanzapine Duration: 2.0 months
Depression Olanzapine (Svestka J SO, 2000) Czech Republic	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: HAM-D ≥ 21 Exclusion criteria: NR	Control-dosage not reported Olanzapine-18.25 mg/day average final dose Duration: 1.0 month
Depression Olanzapine (Tohen M et al., 2002) US	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: YMRS ≥ 20, Age 18-75 Exclusion criteria: Medically significant disorders, Alcohol or substance abuse or dependency, Atypical antipsychotics sensitivity, Sensitivity to mood stabilizer, Treatment with lithium, anticonvulsant, or antipsychotic within 24 hrs,	Divalproex- 1,402 mg/day average final dose Olanzapine-17.4 mg/day average final dose Duration: 0.8 month
Depression Olanzapine (Tohen M et al., 2005) Canada, Europe, Australia/NZ, South Africa HGHT Study	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: YMRS ≥ 20, 2 manic or mixed episodes in the preceding 6 years Exclusion criteria: Medically significant disorders, Alcohol or substance abuse or dependency, Depot neuroleptic within 6 weeks, Suicidal or violent, Previous sensitivity or unresponsiveness to stuffy drug	Lithium-1102.7 mg/day average final dose Olanzapine-11.9 mg/day average final dose Duration: 13.0 months
Depression Olanzapine (Tollefson GD et al., 1997) US & Europe	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: Age ≥ 18, BPRS ≥ 18 Exclusion criteria: NR	Haloperidol-11.8 mg/day average final dose Olanzapine-13.2 mg/day average final dose Duration: 1.5 months

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Dementia Olanzapine & Risperidone (Gareri P et al., 2004) Western Europe	Design: RCT Setting: NR Jadad: 3	Inclusion criteria: Age ≥ 65 Exclusion criteria: NR	Promazine-50-100 mg/day flexible dose Risperidone-1-2 mg/day flexible dose Olanzapine-5-10 mg/day flexible dose Duration: 2.0 months
Depression Quetiapine (Altamura AC et al., 2003) Western Europe	Design: RCT Setting: Single center Jadad: 2	Inclusion criteria: Previous depressed, manic, or mixed episode, CGI ≥ moderate severity, MMSE ≤ 23, PANSS ≥ 50, Stable on risperidone, PANSS with score ≥ 4 on at least 2 items on positive symptoms subscale, Exclusion criteria: Abnormal laboratory results, HIV dementia	Control-dosage not reported Quetiapine-157.7 mg/day average final dose Duration: 12.0 months
Depression Risperidone (Muller-Siecheneder F et al., 1998) Western Europe	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age 18-65, PANSS ≥ 60, PANSS with score ≥ 4 on at least 2 items on positive symptoms subscale, BRMS ≥ 15 with ≥3 on its depression item, Coexisting major depressive, paranoid and/or hallucinatory symptoms Exclusion criteria: Suicidal or violent, Severe internal or neurological disease, Abnormal laboratory results, Allergic or toxic reactions to psychotropic medications, Participation in previous clinical trial within 4 weeks, Pregnant, Lactating,	Haloperidol-9.0 mg/day average final dose, Amitriptyline- 180 mg Risperidone-6.9 mg/day average final dose Duration: 1.5 months
Depression Risperidone (Shelton RC et al., 2004) US	Design: RCT Setting: NR Jadad: 4	Inclusion criteria: Treatment = lithium, carbamazepine, or valproate at therapeutic level, HAM-D ≥ 18, YMRS ≤ 8, Medically stable Exclusion criteria: Current psychosis, Alcohol or substance abuse or dependency, Other psychotropic herbs, History of non-affective disorder	Paroxetine- 20-40 mg/day Risperidone-2.15 mg/day average final dose Risperidone-1.16 mg/day average final dose, Paroxetine-20-40 mg/day Duration: 3.0 months

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Dementia Risperidone (Weiser M et al., 2002) NR The Rivastigmine-Risperidone Study	Design: RCT Setting: Multi-center Jadad: 1	Inclusion criteria: MMSE = 5-26, NPI/NH ≥ 3 Exclusion criteria: NR	Control-dosage not reported, Rivastigmine- 3 -12 mg/day Risperidone-0.8 mg/day average final dose Risperidone-0.8 mg/day average final dose, Rivastigmine, 3-12 mg/day Risperidone-0.8 mg/day average final dose, Rivastigmine- 3-12 mg/day Duration: 5.0 months
Personality Disorder Olanzapine (Zanarini MC et al., 2004) US	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: Age 18-40 Exclusion criteria: Fluoxetine successful treatment, Olanzapine successful treatment, Medically significant disorders, Seizure disorder or epilepsy or risk, Psychotropic medications, Alcohol or substance abuse or dependency, Suicidal or violent, Major depressive disorder	Fluoxetine- 15.0 mg/day average final dose Olanzapine-3.3 mg/day average final dose Olanzapine-3.2 mg/day average final dose, Fluoxetine- 12.7 mg/day average final dose Duration: 2.0 months
Tourettes Risperidone (Bruggeman R et al., 2001) Western Europe, South Africa	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: Age 10-65, TSSS ≥ moderate severity, CGI ≥ moderate severity Exclusion criteria: NR	Pimozide-2.9 mg/day average final dose Risperidone-3.8 mg/day average final dose Duration: 3.0 months
Tourettes Risperidone (Gaffney GR et al., 2002) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Children and adolescents aged 7-17 years, Healthy, able to oral medication, able to adhere to required evaluation schedule Exclusion criteria: Epilepsy, Neurological disorder, Pregnant, Abnormal laboratory results	Risperidone-1.5 mg/day average final dose Clonidine-0.175 mg/day average final dose Duration: 2.0 months
Dementia, Depression and Agitation Olanzapine (Kinon BJ et al., 2005) US	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: NR Exclusion criteria: Tardive dyskinesia	Typical antipsychotics - dosed per package insert Olanzapine - 5.9 mg/day average final dose Duration: 12.0 months

≥Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)
Depression Aripiprazole (Kasper S et al., 2003) US, Europe, other countries NOS	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age 18-65, Male or female, Experiencing an acute relapse, PANSS ≥ 60, PANSS with score ≥ 4 on at least 1 items on positive symptoms subscale, Previous response to antipsychotics, Continuous outpatient treatment ≥ 3 month period during previous year Exclusion criteria: Pregnant, Lactating, Resistant to antipsychotic treatment, Suicidal or violent, Alcohol or substance abuse or dependency, Neurological disorder, Investigational drug use ≥ 4 wks, Psychiatric disorder, not including primary conditioned studied	Haloperidol - 8.90 mg/day average final dose Aripiprazole - 29.01 mg/day average final dose Duration: 13.0 months
Depression Olanzapine (Corya SA et al., 2005) NR	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: MMSE = 14-26, Age ≥ 18, CGI ≥ 4, MADRS ≥ 30% reduction at week 7, At least 1 SSRI treatment failure ≥ 6 weeks at therapeutic dose Exclusion criteria: Bipolar disorder, Psychotic disorder, Schizophrenia, Schizoaffective disorder, PTSD, Major depressive disorder with seasonal pattern, Dissociative disorder	Fluoxetine-37.5 mg/day average final dose Velanfaxine - 275.4 mg/day average final dose Olanzapine - 7.9 mg/day average final dose Olanzapine - 1 mg/day average final dose, Fluoxetine - 5 mg/day average final dose Olanzapine - 7.9 mg/day average final dose, Fluoxetine - 37.5 mg/day average final dose Duration: 3.0 months
Depression Olanzapine (Dunner DL et al., 2005) NR	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: MADRS ≥ 20, CGI ≥ 4, At least 1 manic or mixed episode requiring treatment with mood stabilizer or antipsychotic Exclusion criteria: Suicidal or violent, Alcohol or substance abuse or dependency, Previous exposure to study drug, Previous failure or responded poorly to olanzapine, antidepressants or lamotrigine, Olanzapine + antidepressants treatment, Lamotrigine treatment, YMRS ≥ 15	Lamotrigine - 150-200 mg/day flexible dos Olanzapine - 6-12 mg/day flexible dose, Fluoxetine - 25-50 mg/day flexible dose Duration: 6.3 months

≥Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**
Depression Olanzapine (Shelton RC et al., 2005) US & Canada	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: At least 1 SSRI treatment failure > 4 weeks at therapeutic dose, Nortriptyline treatment failure after week 7, MADRS ≥ 20 Exclusion criteria: BPRS positive item score ≥ 3, Pregnant, Lactating, ECT treatment history or requiring during study	Fluoxetine - 35.8 mg/day average final dose Nortriptyline - 103.5 mg/day average final dose Olanzapine - 8.3 mg/day average final dose Olanzapine - 8.5 mg/day average final dose, Fluoxetine - 36.5 mg/day average final dose Duration: 2.0 months
Tourettes Risperidone (Gilbert DL et al., 2004) US	Design: CCT, Crossover Setting: Multi-center Jadad: 5	Inclusion criteria: Age 7-17, CGI ≥ 4 of tic severity score Exclusion criteria: Psychotic disorder, Alcohol or substance abuse or dependency, Pervasive developmental disorder, Eating disorders, Transient tic disorder, Medically significant disorders, Abnormal laboratory results, Sexually active females of child bearing age not using an effective contraceptive method	Pimozide - 4 mg/day average final dose Risperidone - 2 mg/day average final dose Duration: 3.0 months

Condition, Drug **Author, Year** **Country, Trial named**	**Run-in period/** **Randomization Method** **Wash-out period/** **Randomization Method**	**Allowed other medications**	**Method of outcome assessment** **Timing of assessment**	**Age mean/Age range** **Gender** **Ethnicity**
Autism Olanzapine (Malone RP et al., 2001) US	None None	NR	Assessed at baseline and 6 weeks: CGI, CPRS	8/5-12 67% male Caucasian, African-American, Hispanic
Dementia and Agitation Olanzapine (Meehan KM et al., 2002) US, Russia	None None	NR	Assessed at baseline and 24 hours: PANSS, CMAI, ACES, BPRS, MMSE, CGI	78/54-97 39% male Caucasian, NOS
Dementia and Agitation Quetiapine (Ballard C et al., 2005) UK	None None	NR	Assessed at baseline and 26 weeks: CMAI, SIB	84/NR 20% male NR
Dementia and Agitation Risperidone (Chan WC et al., 2001) China	None 7-14 dy of Psychotropics, Antiparkinsonians for randomization not described	Acetylcholinesterase inhibitors, Benzhexol, Benzodiazepines, Chloral hydrate	Assessed at baseline and 12 weeks: CMAI, BEHAVE-AD, FAST, MMSE	81/NR 28% male Chinese
Dementia and Agitation Risperidone (De Deyn PP et al., 1999) Canada, UK, Europe	None 1 wk of Psychotropics, for patients who completed the wash-out period	NR	Assessed at baseline and 12 weeks: BEHAVE-AD, CMAI, CGI	Median age 81/56-97 44% male Caucasian, African-American, Asian
Dementia and Agitation Risperidone (Suh GH et al., 2004) Korea	None 1 wk of Psychotropics for randomization not described	NR	Assessed at baseline and 15 weeks: BEHAVE-AD, CMAI, CGI	81/65-97 18% male Korean
Depression Olanzapine (David S JBAKWP, 2002) NR	None None	NR	Assessed at baseline and 999 frequency not reported: Adverse events	NR/NR NR NR

Condition, Drug **Author, Year** **Country, Trial named**	**Run-in period/** **Randomization Method** **Wash-out period/** **Randomization Method**	**Allowed other medications**	**Method of outcome assessment** **Timing of assessment**	**Age mean/Age range** **Gender** **Ethnicity**
Depression Olanzapine (McEvoy J et al.,) US, Canada, UK, Europe HGDH Study	None 12-14 dy of Antipsychotics for randomization not described	Anticholinergic medications, Benzodiazepines	Assessed at baseline and 104 weeks: CGI, MADRS, PANSS	24/NR 82% male Caucasian, African-American, Hispanic, Asian, NOS
Depression Olanzapine (Shelton RC et al., 2001)[1] (Tohen M et al., 1999) US	6 wk of Fluoxetine for non-responders None	NR	Assessed at baseline and 8 weeks: MADRS, HAM_D_HDRS, CGI	42/NR 25% male Caucasian, NOS
Depression Olanzapine (Street JS et al., 2000)[1] (Street JS et al., 2000)[1] (Satterlee WG et al., 1995) NR	None None	NR	Assessed at baseline and 8 weeks: BEHAVE-AD, Extrapyramidel side effects	79/64-94 33% male Caucasian
Depression Olanzapine (Svestka J SO, 2000) Czech Republic	4.7 dy of Placebo for randomization not described None	Amitriptyline	Assessed at baseline and 4 weeks: HAM_D_HDRS, CGI, MADRS	50/NR NR NR
Depression Olanzapine (Tohen M et al., 2002) US	None None	Anticholinergic medications, Benzodiazepines	Assessed at baseline and 3 weeks: YMRS, HAM_D_HDRS	41/18-75 43% male Caucasian, NOS
Depression Olanzapine (Tohen M et al., 2005) Canada, Europe, Australia/NZ, South Africa HGHT Study	None 6-12 wk of Antipsychotics, Antidepressants, Anticonvulsants for patients in symptomatic remission	Anticholinergic medications, Benzodiazepines	Assessed at baseline and 52 weeks: HAM_D_HDRS, YMRS	42/NR 47% male Caucasian, NOS
Depression Olanzapine (Tollefson GD et al., 1997) US & Europe	None 2-9 dy of Placebo for symptomatic patients	Anti-EPS medications, Benzodiazepines	Assessed at baseline and 6 weeks: BPRS, PANSS, MADRS, CGI	39/NR 65% male Caucasian, African-American, Hispanic, Asian, NOS

Condition, Drug Author, Year Country, Trial named	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/Age range Gender Ethnicity**
Dementia Olanzapine & Risperidone (Gareri P et al., 2004) Western Europe	None 10 dy of Placebo for randomization not described	NR	Assessed at baseline and 8 weeks: NPI	79/NR 45% male NR
Depression Quetiapine (Altamura AC et al., 2003) Western Europe	None None	Valproate, Lithium, Gabapentin	Assessed at baseline and 12 months: BPRS, CGI, YMRS, HAM_D_HDRS	52/NR 43% male NR
Depression Risperidone (Muller-Siecheneder F et al., 1998) Western Europe	None 3 dy of Antipsychotics, Antidepressants for randomization not described	Anti-EPS medications, Benzodiazepines	Assessed at baseline and 6 weeks: PANSS, BPRS, BRMES, CGI	NR/19-63 38% male NR
Depression Risperidone (Shelton RC et al., 2004) US	None None	Anticonvulsants, Carbamazepine, Divalproex, Lithium, Topiramate	Assessed at baseline and 12 weeks: HAM_D_HDRS, MADRS, BDI, CGI, YMRS	36/NR 50% male NR
Dementia Risperidone (Weiser M et al., 2002) NR The Rivastigmine-Risperidone Study	None None	Lorazepam	Assessed at baseline and 20 weeks: NPI, ADAS-cog	75/NR 50% male NR
Personality Disorder Olanzapine (Zanarini MC et al., 2004) US	None None	NR	Assessed at baseline and 8 weeks: OAS-M, MADRS	23/NR 0% male Caucasian, NOS
Tourettes Risperidone (Bruggeman R et al., 2001) Western Europe, South Africa	None 2 wk for oral antipsychotics and antidepressants, A minimum of 1 treatment cycle for depot medication, At least 5 wks for fluoxetine, for randomization not described	Antiparkinson medication and benzodiazepine use was limited during treatment	Assessed at baseline and 12 weeks: TSSS, CGI, PGI, YBOCS, HAM_A, GAF	NR/11-50 88% male NR

Condition, Drug **Author, Year** **Country, Trial named**	**Run-in period/** **Randomization Method** **Wash-out period/** **Randomization Method**	**Allowed other medications**	**Method of outcome assessment** **Timing of assessment**	**Age mean/Age range** **Gender** **Ethnicity**
Tourettes Risperidone (Gaffney GR et al., 2002) US	7-14 dy of Placebo/Randomization not described	None	Assessed at baseline and 8 weeks: Yale Global Tic, YBOCS, ADHDRS, CGI, MOVES, HAM_D_HDRS	11/7-17 90% male NR
Dementia, Depression and Agitation Olanzapine (Kinon BJ et al., 2005) US	6 wk of Olanzapine and typical antipsychotics. Patients who remained without tardive dyskinesia proceed to randomization None	Not reported	Assessed at baseline and 1 years: Adverse events	79 / NR 48% male NR
Depression Aripiprazole (Kasper S et al., 2003) US, Europe, other countries NOS	None ≥ 5 dy of placebo for patients still eligible after washout	Anticholinergic medications, Anti-EPS medications	Assessed at baseline and 52 weeks: PANSS, MADRS, CGI, Extrapyramidel side effects	37 / NR 59% male NR
Depression Olanzapine (Corya SA et al., 2005) NR	7 wk of Venlafaxine for randomization not described None	Benzodiazepines	Assessed at baseline and 12 weeks: MADRS, CGI, HAM_A, BPRS, Extrapyramidel side effects	46 / NR 28% male Caucasian, NOS
Depression Olanzapine (Dunner DL et al., 2005) NR	None None	Not reported	Assessed at baseline and 25 weeks: CGI, MADRS, YMRS, BSI	37 / NR 40% male Caucasian, NOS
Depression Olanzapine (Shelton RC et al., 2005) US & Canada	7 wk of Nortriptyline for patients resistant to nortriptyline treatment 2-7 dy of ND for randomization not described	Lorazepam as long as it was not within 8 hours of psychiatric evaluation	Assessed at baseline and 8 weeks: MADRS, CGI, HAM_A, BPRS, Extrapyramidel side effects	42 / NR 32% male Caucasian, NOS
Tourettes Risperidone (Gilbert DL et al., 2004) US	2 wk of placebo, randomization not described 2 wk of placebo after cross-over	Not reported	Assessed at baseline and 4 weeks: Yale Global Tic, CGI, TSSR, Extrapyramidel side effects	11 / 7-17 79% male Caucasian, African-American

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Autism Olanzapine (Malone RP et al., 2001) US	NR/13/12	1/0/12	Autism-Change in CGI-S at 6 weeks: Haloperidol vs Olanzapine-SMD = -0.233(-1.369,0.904)	Monitored
Dementia and Agitation Olanzapine (Meehan KM et al., 2002) US, Russia	331/272/ 272	NR/NR/NR	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored, clinical observation and exam
Dementia and Agitation Quetiapine (Ballard C et al., 2005) UK	282/93/93	20/1/74	Dementia_agitation-Change in CMAI at 6 weeks: Placebo vs Quetiapine-SMD = 0.276(-0.25, 0.803) Dementia_agitation-Change in CMAI at 6 weeks: Rivastigmine vs Quetiapine-SMD = -0.051(-0.601,0.499)	NR
Dementia and Agitation Risperidone (Chan WC et al., 2001) China	NR/58/58	3/NR/55	Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Haloperidol vs Risperidone-SMD = 0.057(-0.472,0.585) Dementia_psychosis-Change in BEHAVE-AD (psychosis) at 12 weeks: Haloperidol vs Risperidone-SMD = -0.383(-0.917,0.15)	Monitored, reported by patient

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Dementia and Agitation Risperidone (De Deyn PP et al., 1999) Canada, UK, Europe	371/344/ 344	121/0/NR	Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Placebo vs Risperidone-SMD = -0.702(-1.041, -0.362) Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Haloperidol vs Risperidone-SMD = -0.401(-0.727,-0.075) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Placebo vs Risperidone-SMD = -0.427(-0.76, -0.094) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Haloperidol vs Risperidone-SMD = -0.221(-0.545,0.102)	Monitored
Dementia and Agitation Risperidone (Suh GH et al., 2004) Korea	280/120/ 120	6/0/117	Dementia_global-Change in BEHAVE-AD-K (total) at 8 weeks: Haloperidol vs Risperidone-SMD = -0.558(-0.923,-0.193)	Monitored
Depression Olanzapine (David S JBAKWP, 2002) NR	NR/1054/NR	NR/NR/NR	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Depression Olanzapine (McEvoy J et al.,) US, Canada, UK, Europe HGDH Study	NR/263/ 263	NR/14/41	Depression_mood-Change in MADRS at 12 weeks: Haloperidol vs Olanzapine-SMD = -0.218(-0.46,0.025) Depression_severity-Change in CGI-S at 12 weeks: Haloperidol vs Olanzapine-WMD = -0.15(-0.352,0.052)	Monitored
Depression Olanzapine (Shelton RC et al., 2001)' (Tohen M et al., 1999) US	34/33/28	NR/1/22	Insufficient statistics for effect-size calculation.	NR
Depression Olanzapine (Street JS et al., 2000)' (Street JS et al., 2000)' (Satterlee WG et al., 1995) NR	NR/NR/ 238	NR/NR/NR	Insufficient statistics for effect-size calculation.	NR
Depression Olanzapine (Svestka J SO, 2000) Czech Republic	NR/40/40	0/0/40	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	NR
Depression Olanzapine (Tohen M et al., 2002) US	330/251/ 251	84/0/251	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored
Depression Olanzapine (Tohen M et al., 2005) Canada, Europe, Australia/NZ, South Africa HGHT Study	543/431/ 431	257/3/431	Depression_mood Follow-up time greater than 48 weeks	Monitored

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Depression Olanzapine (Tollefson GD et al., 1997) US & Europe	2223/1996/1996	773/26/1996	Depression_mood-Change in MADRS at 6 weeks: Haloperidol vs Olanzapine-SMD = -0.389(-0.502,-0.275) Depression_severity-Change in CGI-S at 6 weeks: Haloperidol vs Olanzapine-WMD = -0.3(-0.379,-0.221)	Monitored, elicited by investigator, medical record, clinical exam
Depression Olanzapine & Risperidone (Gareri P et al., 2004) Western Europe	NR/60/60	0/0/60	Insufficient statistics for effect-size calculation.	Monitored
Depression Quetiapine (Altamura AC et al., 2003) Western Europe	NR/28/28	0/0/28	Depression_mood Follow-up time greater than 48 weeks Depression_severity Follow-up time greater than 48 weeks	Monitored
Depression Risperidone (Muller-Siecheneder F et al., 1998) Western Europe	NR/123/ 123	33/0/90	Depression_mood-Change in BRMES at 6 weeks: Haloperidol + amitriptyline vs Risperidone-SMD = -0.427(-0.828,-0.026)	Monitored, elicited by investigator

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Depression Risperidone (Shelton RC et al., 2004) US	NR/30/30	9/2/30	Depression_improvement-Change in CGI-I at 12 weeks: Paroxetine + placebo vs Risperidone + placebo-WMD = 0.7(-0.62,2.02) Depression_improvement-Change in CGI-I at 12 weeks: Paroxetine + placebo vs Risperidone + paroxetine-WMD = -0.7 (-1.805,0.405) Depression_mood-Change in MADRS at 12 weeks: Paroxetine + placebo vs Risperidone + placebo-SMD = 0.479(-0.656, 1.614) Depression_mood-Change in MADRS at 12 weeks: Paroxetine + placebo vs Risperidone + paroxetine-SMD = 0.272(-0.792,1.336)	Monitored
Depression Risperidone (Weiser M et al., 2002) NR The Rivastigmine-Risperidone Study	NR/90/85	NR/NR/58	Dementia_global-Change in NPI-12 at 20 weeks: Rivastigmine vs Risperidone-SMD = -0.918(-1.926,0.089) Dementia_global-Change in NPI-12 at 20 weeks: Rivastigmine vs Rivastigmine + risperidone-SMD = -0.956(-1.752,-0.161) Dementia_global-Change in NPI-12 at 20 weeks: Rivastigmine vs Risperidone + rivastigmine-SMD = -0.798(-1.903,0.308)	Monitored, reported by patient

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Personality Disorder Olanzapine (Zanarini MC et al., 2004) US	NR/45/45	2/1/1942	Personality Disorder-Change in MADRAS at 8 weeks: Fluoxetine vs Olanzapine-SMD = -0.086(-0.818,0.646) Personality Disorder-Change in MADRAS at 8 weeks: Fluoxetine vs Olanzapine + fluoxetine-SMD = -0.286(-1.059,0.487)	Monitored, elicited by investigator
Tourettes Risperidone (Bruggeman R et al., 2001) Western Europe, South Africa	NR/51/51	8/1/50	Tourettes-Change in CGI-I at 12 weeks: Pimozide vs Risperidone-SMD = 0(-0.555,0.555)	Monitored, reported by patient
Tourettes Risperidone (Gaffney GR et al., 2002) US	24/21/21	1/0/21	Tourettes-Change in CGI-S at 8 weeks: Clonidine vs Risperidone-SMD = 0(-0.895,0.895)	Monitored
Dementia, Depression and Agitation Olanzapine (Kinon BJ et al., 2005) US	NR/293/293	148/4/141	No outcomes of interest to calculate effect size.	Monitored
Depression Aripiprazole (Kasper S et al., 2003) US, Europe, other countries NOS	NR/1294/1294	NR/NR/1283	Depression_mood Follow-up time greater than 48 weeks.	Monitored, elicited by investigator, reported by patient, .
Depression Olanzapine (Corya SA et al., 2005) NR	807/483/483	NR/10/365	Insufficient statistics for effect-size calculation.	Monitored

Condition, Drug Author, Year Country, Trial named	Screened/Eligible/Enrolled	Withdrawn/Lost to FU/Analyzed	Results	Method of adverse events assessment
Depression Olanzapine (Dunner DL et al., 2005) NR	NR/410/410	189/84/393	Depression_mood and Depression_severity not a comparison of interest.	Monitored
Depression Olanzapine (Shelton RC et al., 2005) US & Canada	946/500/500	NR/17/500	Depression_severity-Change in CGI-S at 8 weeks: Fluoxetine vs Olanzapine-WMD = 0.1(-0.146,0.346) Depression_severity-Change in CGI-S at 8 weeks: Nortriptlyline vs Olanzapine-WMD = 0(-0.306,0.306)	Monitored
Tourettes Risperidone (Gilbert DL et al., 2004) US	NR/19/19	1/1/2017	Tourettes Crossover study.	Monitored

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Autism Olanzapine (Malone RP et al., 2001) US	Haloperidol vs Olanzapine: Ataxia: 16.7%(1/6) vs 0.0%(0/6) Behavioral toxicity: 33.3%(2/6) vs 0.0%(0/6) Drowsiness: 33.3%(2/6) vs 83.3%(5/6) Dry mouth: 16.7%(1/6) vs 16.7%(1/6) Dyskinesia: 0.0%(0/6) vs 0.0%(0/6) Enuresis: 16.7%(1/6) vs 16.7%(1/6) Insomnia: 0.0%(0/6) vs 16.7%(1/6) Nausea/vomiting: 0.0%(0/6) vs 33.3%(2/6) Rash: 16.7%(1/6) vs 0.0%(0/6) Rigidity: 16.7%(1/6) vs 0.0%(0/6) Tachycardia: 16.7%(1/6) vs 0.0%(0/6) Transient mild rigidity: 16.7%(1/6) vs 0.0%(0/6) Weight gain: 83.3%(5/6) vs 100.0%(6/6) Weight loss: 16.7%(1/6) vs 0.0%(0/6) Weight change in lbs: Haloperidol-6 people (3.2 mean,4.9 SD) vs Olanzapine-6 people (9 mean,3.5 SD)	Haloperidol vs Olanzapine: Withdrawals: 0.0%(0/6) vs 0.0%(0/6) Withdrawals due to adverse events: 0.0%(0/6) vs 0.0%(0/6)
Dementia and Agitation Olanzapine (Meehan KM et al., 2002) US, Russia	Placebo vs Lorazepam 1.0 mg/d vs Olanzapine 2.5 mg/d vs Olanzapine 5.0 mg/d: Accidental injury: 0.0%(0/67) vs 4.4%(3/68) vs 1.4%(1/71) vs 3.0%(2/66) ECG abnormal: 0.0%(0/67) vs 0.0%(0/68) vs 1.4%(1/71) vs 3.0%(2/66) Headache: 0.0%(0/67) vs 1.5%(1/68) vs 2.8%(2/71) vs 3.0%(2/66) Hypertension: 1.5%(1/67) vs 2.9%(2/68) vs 0.0%(0/71) vs 3.0%(2/66) Sinus bradycardia: 3.0%(2/67) vs 0.0%(0/68) vs 0.0%(0/71) vs 0.0%(0/66) Somnolence: 3.0%(2/67) vs 10.3%(7/68) vs 4.2%(3/71) vs 3.0%(2/66) Vasodilation: 0.0%(0/67) vs 0.0%(0/68) vs 0.0%(0/71) vs 3.0%(2/66)	Placebo vs Lorazepam 1.0 mg/d vs Olanzapine 2.5 mg/d vs Olanzapine 5.0 mg/d: Withdrawals: 13.4%(9/67) vs 17.6%(12/68) vs 11.3%(8/71) vs 10.6%(7/66) Withdrawals due to adverse events: 0.0%(0/67) vs 0.0%(0/68) vs 0.0%(0/71) vs 0.0%(0/66)
Dementia and Agitation Quetiapine (Ballard C et al., 2005) UK	Placebo vs Rivastigmine vs Quetiapine: Death: 3.2%(1/31) vs 0.0%(0/31) vs 0.0%(0/31) Serious adverse events: 3.2%(1/31) vs 0.0%(0/31) vs 0.0%(0/31)	Placebo vs Rivastigmine vs Quetiapine: Withdrawals: 3.2%(1/31) vs 32.3%(10/31) vs 25.8%(8/31) Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Dementia and Agitation Risperidone (Chan WC et al., 2001) China	Haloperidol vs Risperidone: Acute retention of urine: 0.0%(0/29) vs 3.4%(1/29) Constipation: 6.9%(2/29) vs 0.0%(0/29) Drug-related day-time sleepiness: 10.3%(3/29) vs 0.0%(0/29) Nausea: 0.0%(0/29) vs 3.4%(1/29) Somnolence: 3.4%(1/29) vs 0.0%(0/29)	Haloperidol vs Risperidone: Withdrawals: 3.4%(1/29) vs 6.9%(2/29) Withdrawals due to adverse events: 3.4%(1/29) vs 0.0%(0/29)
Dementia and Agitation Risperidone (De Deyn PP et al., 1999) Canada, UK, Europe	Placebo vs Haloperidol vs Risperidone: At least one adverse event: 72.8%(83/114) vs 80.0%(92/115) vs 76.5%(88/115) Somnolence: 4.4%(5/114) vs 18.3%(19/115) vs 12.2%(14/115)	Placebo vs Haloperidol vs Risperidone: Withdrawals: 35.1%(40/114) vs 29.6%(34/115) vs 40.9%(47/115) Withdrawals due to adverse events: Not reported
Dementia and Agitation Risperidone (Suh GH et al., 2004) Korea	Adverse events not reported.	Haloperidol vs Risperidone: Withdrawals: 1.7%(1/60) vs 3.3%(2/60) Withdrawals due to adverse events: 1.7%(1/60) vs 3.3%(2/60)
Depression Olanzapine (David S JBAKWP, 2002) NR	No adverse events reported.	Data not reported by intervention group.
Depression Olanzapine (McEvoy J et al.,) US, Canada, UK, Europe HGDH Study	Haloperidol vs Olanzapine: Akathisia: 30.3%(39.996/132) vs 13.0%(17.03/131) Dystonia: 13.0%(17.16/132) vs 0.0%(0/131) Emotional liability: 5.3%(6.996/132) vs 7.6%(9.956/131) Epistaxis: 0.0%(0/132) vs 4.6%(6.026/131) Extrapyramidal syndrome: 15.2%(20.064/132) vs 4.6%(6.026/131) Increased appetite: 6.1%(8.052/132) vs 16.8%(22.008/131) Joint disorder: 12.1%(15.972/132) vs 3.1%(4.061/131) Nervousness: 38.6%(50.952/132) vs 20.6%(26.986/131) Vomiting: 12.9%(17.028/132) vs 7.6%(9.956/131) Weight gain: 18.9%(24.948/132) vs 43.5%(56.985/131) Weight change in kg: Haloperidol-132 people (4.12 mean, SD NR) vs Olanzapine-131 people (10.47 mean, SD NR)	Haloperidol vs Olanzapine: Withdrawals: 91.1%(119/132) vs 78.6%(103/131) Withdrawals due to adverse events: 13.6%(18/132) vs 5.3%(7/131)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine (Shelton RC et al., 2001)' (Tohen M et al., 1999) US	No adverse events reported. Weight change in kg: Fluoxetine-10 people (0.88 mean,1.33 SD) vs Olanzapine-8 people (6.07 mean,2.57 SD) vs Olanazpine + Fluoxetine-10 people (6.67 mean,4.54 SD)	Fluoxetine vs Olanzapine vs Olanazpine + Fluoxetine: Withdrawals: 30.0%(3/10) vs 25.0%(2/8) vs 10.0%(1/10) Withdrawals due to adverse events: 0.0%(0/10) vs 12.5%(1/8) vs 0.0%(0/10)
Depression Olanzapine (Street JS et al., 2000)' (Street JS et al., 2000)' (Satterlee WG et al., 1995) NR	No adverse events reported.	Haloperidol vs Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
Depression Olanzapine (Svestka J SO, 2000) Czech Republic	Amitriptyline vs Olanzapine: Hyperprolactinemia: 5.0%(1/20) vs 30.0%(6/20) Tachycardia: 50.0%(10/20) vs 20.0%(4/20) Undesirable effects: 90.0%(18/20) vs 60.0%(12/20)	Amitriptyline vs Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine (Tohen M et al., 2002) US	Divalproex vs Olanzapine: Agitation: 11.1%(14/126) vs 11.2%(14/125) Asthenia: 13.5%(17/126) vs 16.0%(20/125) Constipation: 11.9%(15/126) vs 14.4%(18/125) Decreased platelet count: 8.0%(10.08/126) vs 0.0%(0/125) Diarrhea: 13.5%(17/126) vs 6.4%(8/125) Dizziness: 11.9%(15/126) vs 16.0%(20/125) Dry mouth: 6.3%(8/126) vs 33.6%(42/125) Dyspepsia: 11.1%(14/126) vs 14.4%(18/125) Headache: 23.0%(29/126) vs 22.4%(28/125) Increased ALT/SGPT values: 0.0%(0/126) vs 5.1%(6.375/125) Increased appetite: 2.4%(3/126) vs 12.0%(15/125) Nausea: 28.6%(36/126) vs 10.4%(13/125) Neck rigidity: 1.6%(2/126) vs 7.2%(9/125) Nervousness: 16.7%(21/126) vs 10.4%(13/125) Pain: 14.3%(18/126) vs 13.6%(17/125) Sleep disorder: 0.8%(1/126) vs 5.6%(7/125) Somnolence: 20.6%(26/126) vs 39.2%(49/125) Speech disorder: 0.8%(1/126) vs 8.0%(10/125) Tongue edema: 0.0%(0/126) vs 4.8%(6/125) Tremor: 3.2%(4/126) vs 9.6%(12/125) Vomiting: 14.3%(18/126) vs 8.0%(10/125) Weight gain: 7.9%(10/126) vs 12.0%(15/125) Weight change in kg: Divalproex-126 people (0.9 mean, 2.5 SD) vs Olanzapine-125 people (2.5 mean,2.5 SD)	Divalproex vs Olanzapine: Withdrawals: 22.2%(28/126) vs 23.2%(29/125) Withdrawals due to adverse events: 7.1%(9/126) vs 9.6%(12/125)
Depression Olanzapine (Tohen M et al., 2005) Canada, Europe, Australia/NZ, South Africa HGHT Study	Lithium vs Olanzapine: Anxiety: 4.7%(10/214) vs 5.5%(12/217) Death: 0.9%(2/214) vs 0.0%(0/217) Depression not otherwise specified: 11.7%(25/214) vs 20.7%(45/217) Headache not otherwise specified: 5.1%(11/214) vs 4.1%(9/217) Hypersomnia: 0.0%(0/214) vs 2.8%(6/217) Insomnia: 22.4%(48/214) vs 7.8%(17/217) Nausea: 3.7%(8/214) vs 0.5%(1/217) Weight decrease: 5.1%(11/214) vs 3.2%(7/217) Weight increase: 4.7%(10/214) vs 6.5%(14/217) Worsening of mania: 20.6%(44/214) vs 7.8%(17/217) Weight change in kg: Lithium-214 people (-1.4 kg mean, SD) vs Olanzapine-217 people (1.8 kg mean, SD)	Lithium vs Olanzapine: Withdrawals: 67.3%(144/214) vs 53.5%(116/217) Withdrawals due to adverse events: 25.7%(55/214) vs 18.9%(41/217)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine (Tollefson GD et al., 1997) US & Europe	Haloperidol vs Olanzapine: Acute dyskinesia: 8.0%(51/636) vs 2.8%(37/1306) Akathisia: 35.5%(226/636) vs 14.2%(186/1306) Ataxia: 3.1%(20/636) vs 1.7%(22/1306) Blurred vision: 15.1%(96/636) vs 10.6%(139/1306) Chills: 7.5%(48/636) vs 4.3%(56/1306) Conversion symptoms: 2.4%(15/636) vs 1.0%(13/1306) Decreased appetite: 18.1%(115/636) vs 11.4%(149/1306) Difficulty falling asleep: 28.8%(18.3/636) vs 22.9%(299/1306) Difficulty with micturition: 6.1%(39/636) vs 3.6%(47/1306) Drowsiness: 31.3%(199/636) vs 26.0%(339/1306) Dry mouth: 16.2%(103/636) vs 22.2%(290/1306) Early awakening: 24.1%(153/636) vs 15.9%(208/1306) Excessive appetite: 12.4%(79/636) vs 24.0%(313/1306) Heaviness in extremities: 16.4%(104/636) vs 11.5%(150/1306) Hot flashes: 5.7%(36/636) vs 3.4%(45/1306) Hypersalivation: 19.5%(124/636) vs 8.7%(113/1306) Hypertonia: 21.1%(134/636) vs 8.4%(110/1306) Hypokinesia: 13.5%(86/636) vs 5.1%(67/1306) Hypotonia: 4.6%(29/636) vs 2.7%(35/1306) Increased dreams/nightmares: 17.3%(110/636) vs 13.0%(170/1306) Increased perspiration: 13.2%(84/636) vs 6.8%(89/1306) Interrupted sleep: 30.3%(193/636) vs 19.0%(248/1306) Nausea: 13.7%(87/636) vs 10.1%(132/1306) Palpitations: 9.9%(63/636) vs 6.6%(86/1306) Shortened sleep: 24.8%(158/636) vs 15.1%(197/1306) Tremor: 26.3%(167/636) vs 16.5%(216/1306) Vomiting: 9.0%(57/636) vs 5.1%(67/1306) Weight change in kg: Haloperidol-636 people (0.02 mean,2.79 SD) vs Olanzapine-1306 people (1.88 mean,3.54 SD)	Haloperidol vs Olanzapine: Withdrawals: 53.2%(351/660) vs 33.6%(448/ 1336) Withdrawals due to adverse events: 7.3%(48/660) vs 4.5%(60/1336)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine & Risperidone (Gareri P et al., 2004) Western Europe	Promazine vs Risperidone vs Olanzapine: Abdominal pain: 0.0%(0/20) vs 4.0%(0.8/20) vs 0.0%(0/20) Akathisia: 0.0%(0/20) vs 0.0%(0/20) vs 4.0%(0.8/20) Arterial hypotension: 35.0%(7/20) vs 20.0%(4/20) vs 0.0%(0/20) Asthenia: 0.0%(0/20) vs 8.0%(1.6/20) vs 0.0%(0/20) Confusion: 15.0%(3/20) vs 0.0%(0/20) vs 0.0%(0/20) Constipation: 35.0%(7/20) vs 8.0%(1.6/20) vs 16.0%(3.2/20) Dizziness: 0.0%(0/20) vs 0.0%(0/20) vs 16.0%(3.2/20) Drowsiness: 10.0%(2/20) vs 20.0%(4/20) vs 32.0%(6.4/20) Dyspepsia: 0.0%(0/20) vs 12.0%(2.4/20) vs 0.0%(0/20) EPS: 20.0%(4/20) vs 8.0%(1.6/20) vs 0.0%(0/20) Hyperglycemia (glycemic decompensation): 0.0%(0/20) vs 0.0%(0/20) vs 4.0%(1/20) Increased libido and disinhibition: 0.0%(0/20) vs 4.0%(0.8/20) vs 0.0%(0/20) Insomnia: 0.0%(0/20) vs 4.0%(0.8/20) vs 0.0%(0/20) Nausea (sickness): 5.0%(1/20) vs 0.0%(0/20) vs 0.0%(0/20) Postural hypotension: 0.0%(0/20) vs 0.0%(0/20) vs 8.0%(1.6/20) Sinus tachycardia: 25.0%(5/20) vs 8.0%(1.6/20) vs 0.0%(0/20) Weight gain: 0.0%(0/20) vs 0.0%(0/20) vs 32.0%(6.4/20) Xerostomy: 30.0%(6/20) vs 0.0%(0/20) vs 0.0%(0/20)	Promazine vs Risperidone vs Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: 0.0%(0/20) vs 5.0%(1/20) vs 0.0%(0/20)
Depression Quetiapine (Altamura AC et al., 2003) Western Europe	Other mood stabilizers (lithium, valproate, gabapentin) vs Quetiapine: Constipation: 0.0%(0/14) vs 14.3%(2/14) Sedation: 0.0%(0/14) vs 14.3%(2/14) Weight gain: 14.3%(2/14) vs 0.0%(0/14) Weight change in kg: Other mood stabilizers (lithium, valproate, gabapentin)-14 people (1.79 mean, 1.31 SD) vs Quetiapine-14 people (1.08 mean, 1.26 SD)	Other mood stabilizers (lithium, valproate, gabapentin) vs Quetiapine: Withdrawals: .%(0/14) vs .%(0/14) Withdrawals due to adverse events: 0.0%(0/14) vs 0.0%(0/14)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Risperidone (Muller-Siecheneder F et al., 1998) Western Europe	Haloperidol + Amitriptyline vs Risperidone: Abdominal pain: 3.3%(2/61) vs 0.0%(0/62) Abnormal hepatic function: 16.4%(10/61) vs 4.8%(3/62) Agitation: 1.6%(1/61) vs 3.2%(2/62) Akathisia, tremor: 0.0%(0/61) vs 3.2%(2/62) Constipation: 11.5%(7/61) vs 8.1%(5/62) Dizziness: 1.6%(1/61) vs 3.2%(2/62) Dry mouth: 9.8%(6/61) vs 6.5%(4/62) Dysphagia: 0.0%(0/61) vs 3.2%(2/62) Dystonia, abdominal pain, constipation: 3.3%(2/61) vs 0.0%(0/62) Fatigue: 3.3%(2/61) vs 6.5%(4/62) Hyperprolactinemia: 3.3%(2/61) vs 1.6%(1/62) Hypotension: 6.6%(4/61) vs 0.0%(0/62) Nausea and/or vomiting: 3.3%(2/61) vs 6.5%(4/62) Speech disorder: 1.6%(1/61) vs 1.6%(1/62) Suicidal ideations: 3.3%(2/61) vs 1.6%(1/62) Tachycardia: 3.3%(2/61) vs 1.6%(1/62)	Haloperidol + Amitriptyline vs Risperidone: Withdrawals: 21.3%(13/61) vs 32.3%(20/62) Withdrawals due to adverse events: 11.5%(7/61) vs 21.0%(13/62)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Risperidone (Shelton RC et al., 2004) US	Paroxetine + placebo vs Risperidone + placebo vs Risperidone + paroxetine: Agitation: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Anxiety: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Appetite decrease: 10.0%(1/10) vs 0.0%(0/10) vs 0.0%(0/10) Appetite increase: 20.0%(2/10) vs 20.0%(2/10) vs 20.0%(2/10) Blurred vision: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Constipation: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Depression increased: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Dermatitis: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Diaphoresis: 10.0%(1/10) vs 10.0%(1/10) vs 0.0%(0/10) Diarrhea: 30.0%(3/10) vs 20.0%(2/10) vs 10.0%(1/10) Dizziness: 10.0%(1/10) vs 0.0%(0/10) vs 10.0%(1/10) Dreaming increased: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Dry mouth: 30.0%(3/10) vs 10.0%(1/10) vs 10.0%(1/10) Edema: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Fatigue: 20.0%(2/10) vs 20.0%(2/10) vs 10.0%(1/10) GI distress: 20.0%(2/10) vs 20.0%(2/10) vs 20.0%(2/10) Hair loss: 10.0%(1/10) vs 0.0%(0/10) vs 0.0%(0/10) Headache: 10.0%(1/10) vs 10.0%(1/10) vs 0.0%(0/10) Insomnia: 20.0%(2/10) vs 0.0%(0/10) vs 10.0%(1/10) Joint pain: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Memory problems: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Myoclonus: 0.0%(0/10) vs 10.0%(1/10) vs 0.0%(0/10) Nausea: 20.0%(2/10) vs 0.0%(0/10) vs 0.0%(0/10) Paresthesias: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Salivation increased: 0.0%(0/10) vs 0.0%(0/10) vs 10.0%(1/10) Sexual dysfunction: 20.0%(2/10) vs 0.0%(0/10) vs 30.0%(3/10) Somnolence: 20.0%(2/10) vs 50.0%(5/10) vs 20.0%(2/10) Spaciness: 10.0%(1/10) vs 0.0%(0/10) vs 0.0%(0/10) Tremor: 10.0%(1/10) vs 10.0%(1/10) vs 10.0%(1/10) Urinary tract infection: 10.0%(1/10) vs 0.0%(0/10) vs 0.0%(0/10) Weight gain: 10.0%(1/10) vs 10.0%(1/10) vs 40.0%(4/10)	Paroxetine + placebo vs Risperidone + placebo vs Risperidone + paroxetine: Withdrawals: 20.0%(2/10) vs 50.0%(5/10) vs 40.0%(4/10) Withdrawals due to adverse events: 10.0%(1/10) vs 10.0%(1/10) vs 30.0%(3/10)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Risperidone (Weiser M et al., 2002) NR The Rivastigmine-Risperidone Study	Rivastigmine vs Risperidone vs Rivastigmine + risperidone vs Risperidone + rivastigmine: At least one adverse event: 79.0%(11.06/14) vs 92.0%(11.96/13) vs 87.0%(40.89/47) vs 94.0%(15.04/16) Abdominal pain: 14.0%(1.96/14) vs 0.0%(0/13) vs 6.0%(2.82/47) vs 6.0%(0.96/16) Anorexia: 0.0%(0/14) vs 0.0%(0/13) vs 9.0%(4.23/47) vs 19.0%(3.04/16) Diarrhea: 21.0%(2.94/14) vs 8.0%(1.04/13) vs 13.0%(6.11/47) vs 0.0%(0/16) General weakness: 14.0%(1.96/14) vs 8.0%(1.04/13) vs 21.0%(9.87/47) vs 44.0%(7.04/16) Nausea: 14.0%(1.96/14) vs 8.0%(1.04/13) vs 17.0%(7.99/47) vs 6.0%(0.96/16) Parkinsonism: 0.0%(0/14) vs 15.0%(1.95/13) vs 6.0%(2.82/47) vs 0.0%(0/16) Restlessness: 7.0%(0.98/14) vs 8.0%(1.04/13) vs 11.0%(5.17/47) vs 13.0%(2.08/16) Somnolence/drowsiness: 0.0%(0/14) vs 31.0%(4.03/13) vs 26.0%(12.22/47) vs 31.0%(4.96/16) Vomiting: 21.0%(2.94/14) vs 0.0%(0/13) vs 21.0%(9.87/47) vs 6.0%(0.96/16) Weight loss: 0.0%(0/14) vs 0.0%(0/13) vs 9.0%(4.23/47) vs 13.0%(2.08/16)	Rivastigmine vs Risperidone vs Rivastigmine + risperidone vs Risperidone + rivastigmine: Withdrawals: 30.0%(4.2/14) vs 30.0%(3.9/13) vs 30.0%(14.1/47) vs 62.0%(9.92/16) Withdrawals due to adverse events: 12.0%(1.68/14) vs 15.0%(1.95/13) vs 13.0%(6.11/47) vs 50.0%(8/16)
Personality Disorder Olanzapine (Zanarini MC et al., 2004) US	Fluoxetine vs Olanzapine vs Olanzapine + fluoxetine: Dizziness and headaches: 0.0%(0/14) vs 0.0%(0/16) vs 6.7%(1/15) Mild akathisia: 35.7%(5/14) vs 25.0%(4/16) vs 33.3%(5/15) Mild sedation: 21.4%(3/14) vs 75.0%(12/16) vs 46.7%(7/15) Other serious movement disorders: 0.0%(0/14) vs 0.0%(0/16) vs 0.0%(0/15) Suicide attempt: 7.1%(1/14) vs 0.0%(0/16) vs 0.0%(0/15) Tardive dyskinesia: 0.0%(0/14) vs 0.0%(0/16) vs 0.0%(0/15) Weight change in kg: Fluoxetine-14 people (0.4 mean,2.3 SD) vs Olanzapine-16 people (2.9 mean,2.6 SD) vs Olanzapine + Fluoxetine-15 people (1.4 mean,1.1 SD)	Fluoxetine vs Olanzapine vs Olanzapine + fluoxetine: Withdrawals: 7.1%(1/14) vs 0.0%(0/16) vs 13.3%(2/15) Withdrawals due to adverse events: 0.0%(0/14) vs 0.0%(0/16) vs 6.7%(1/15)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Tourettes Risperidone (Bruggeman R et al., 2001) Western Europe, South Africa	Pimozide vs Risperidone: Depression: 25.0%(6/24) vs 30.8%(8/26) EPS-like adverse events: 33.3%(8/24) vs 15.4%(4/26) Fatigue: 37.5%(9/24) vs 38.5%(10/26) Headache: 8.3%(2/24) vs 19.2%(5/26) Hyperkinesia: 20.8%(5/24) vs 7.7%(2/26) Injuries: 25.0%(6/24) vs 3.8%(1/26) Insomnia: 29.2%(7/24) vs 3.8%(1/26) Somnolence: 41.7%(10/24) vs 46.2%(12/26) Weight gain: 83.3%(20/24) vs 84.6%(22/26) Weight gain & <18 years: 29.2%(7/24) vs 38.5%(10/26) Weight gain & ≥ 18 years: 54.2%(13/24) vs 46.2%(12/26) Weight change in kg: Pimozide-24 people (2.9 mean,1.8-4.1 RANGE) vs Risperidone-26 people (3.9 mean,3.0-4.9 RANGE)	Pimozide vs Risperidone: Withdrawals: 16.7%(4/24) vs 19.2%(5/26) Withdrawals due to adverse events: 8.3%(2/24) vs 15.4%(4/26)
Tourettes Risperidone (Gaffney GR et al., 2002) US	Clonidine vs Risperidone: At least one clinically significant adverse event: 58.0%(6.96/12) vs 33.0%(2.97/9) Dizziness: 17.0%(2/12) vs 11.0%(1/9) Drug-induced parkinsonism: 0.0%(0/12) vs 0.0%(0/9) Dry mouth: 8.0%(1/12) vs 0.0%(0/9) Sedation: 42.0%(5/12) vs 11.0%(1/9) Stiffness: 8.0%(1/12) vs 22.0%(2/9) Weight change in kg: Clonidine-12 people (Mean 0.1, SD 5.9) vs Risperidone-9 people (2.1 mean, SD 2.3)	Clonidine vs Risperidone: Withdrawals: 8.3%(1/12) vs 0.0%(0/9) Withdrawals due to adverse events: 0.0%(0/12) vs 0.0%(0/9)
Dementia, Depression and Agitation Olanzapine (Kinon BJ et al., 2005) US	Typical antipsychotics vs Olanzapine: Anemia: 4.2%(6/143) vs 10.7%(16/150) Apathy: 11.2%(16/143) vs 3.3%(5/150) Cardiovascular effects: 4.3%(6/143) vs 3.4%(5/149) Death: 16.1%(23/143) vs 14.8%(22/149) Skin ulcer: 11.9%(17/143) vs 3.3%(5/150) Weight loss: 23.1%(33/143) vs 11.3%(17/150)	Typical antipsychotics vs Olanzapine: Withdrawals: 55.2%(79/143) vs 46.0%(69/150) Withdrawals due to adverse events: 20.0%(29/143) vs 17.0%(26/150)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Aripiprazole (Kasper S et al., 2003) US, Europe, other countries NOS	Haloperidol vs Aripiprazole: Agitation: 7.0%(30/431) vs 6.0%(53/859) Akathisia: 25.0%(108/431) vs 13.0%(111/859) Anxiety: 12.0%(50/431) vs 13.0%(108/859) Any AE: 87.0%(377/431) vs 78.0%(671/859) Extrapyramidal syndrome: 30.0%(130/431) vs 10.0%(84/859) Headache: 9.0%(38/431) vs 8.0%(65/859) Insomnia: 20.0%(88/431) vs 22.0%(185/859) Psychosis: 16.0%(70/431) vs 18.0%(156/859) Somnolence: 7.0%(32/431) vs 5.0%(43/859) Tremor: 10.0%(41/431) vs 4.0%(34/859) Weight gain: 3.0%(14/431) vs 5.0%(44/859)	Haloperidol vs Aripiprazole: Withdrawals: (NR/431) vs (NR/859) Withdrawals due to adverse events: 32.0%(138/431) vs 24.8%(213/859)
Depression Olanzapine (Corya SA et al., 2005) NR	Fluoxetine vs Venlafaxine vs Olanzapine vs Olanzapine/Flouxetine 1/5 vs Olanzapine/Flouxetine: Asthenia: 8.0%(5/60) vs 8.0%(5/59) vs 18.0%(11/62) vs 8.0%(4.7/59) vs 12.0%(29/243) Death: 0.0%(0/60) vs 0.0%(0/59) vs 0.0%(0/62) vs 0.0%(0/59) vs 0.4%(1/243) Dizziness: 10.0%(6/60) vs 5.0%(3/59) vs 10.0%(6.2/62) vs 22.0%(13/59) vs 14.0%(34/243) Dry mouth: 7.0%(4/60) vs 5.0%(3/59) vs 16.0%(10/62) vs 7.0%(4/59) vs 13.0%(32/243) Extrapyramidal symtoms: (NR/60) vs (NR/59) vs (NR/62) vs (NR/59) vs (NR/243) Headache: 17.0%(10/60) vs 17.0%(10/59) vs 10.0%(6/62) vs 24.0%(14/59) vs 10.0%(24/243) Increased appetite: 7.0%(4/60) vs 5.0%(3/59) vs 16.0%(10/62) vs 14.0%(8/59) vs 16.0%(39/243) Peripheral edema: 0.0%(0/60) vs 2.0%(1/59) vs 8.0%(5/62) vs 5.0%(3/59) vs 11.0%(27/243) Somnolence: 5.0%(3/60) vs 8.0%(5/59) vs 18.0%(11/62) vs 8.0%(5/59) vs 22.0%(53/243) Weight gain: 13.0%(8/60) vs 5.0%(3/59) vs 26.0%(16/62) vs 19.0%(11/59) vs 25.0%(61/243)	Fluoxetine vs Venlafaxine vs Olanzapine vs Olanzapine/Flouxetine 1/5 vs Olanzapine/Flouxetine: Withdrawals: 18.3%(11/60) vs 22.0%(13/59) vs 25.8%(16/62) vs 20.3%(12/59) vs 23.0%(56/243) Withdrawals due to adverse events: 5.0%(3/60) vs 1.7%(1/59) vs 8.1%(5/62) vs 3.4%(2/59) vs 11.9%(29/243)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine (Dunner DL et al., 2005) NR	Lamotrigine vs Olanzapine/Flouxetine: Anxiety: 6.9%(14/205) vs 7.3%(15/205) Arthralgia: 5.9%(12/205) vs 1.5%(3/205) Back pain: 5.9%(12/205) vs 5.4%(11/205) Constipation: 3.9%(8/205) vs 5.4%(11/205) Death: 0.5%(1/205) vs 0.0%(0/205) Diarrhea: 5.9%(12/205) vs 5.9%(12/205) Disturbance in attention: 1.0%(2/205) vs 5.4%(11/205) Dizziness: 9.3%(19/205) vs 14.6%(30/205) Dry mouth: 5.9%(12/205) vs 17.1%(35/205) Fatigue: 6.9%(14/205) vs 9.3%(19/205) Headache: 10.8%(22/205) vs 12.7%(26/205) Increased appetite: 9.3%(19/205) vs 19.5%(40/205) Insomnia: 14.7%(30/205) vs 5.9%(12/205) Irritability: 7.4%(15/205) vs 2.9%(5.9/205) Lethargy: 1.5%(3/205) vs 5.9%(12/205) Nausea: 11.3%(23/205) vs 7.8%(16/205) Peripheral edema: 0.0%(0/205) vs 5.4%(11/205) Rash: 8.8%(18/205) vs 5.4%(11/205) Sedation: 2.9%(6/205) vs 14.1%(29/205) Somnolence: 9.3%(19/205) vs 21.0%(43/205) Tremor: 1.5%(3/205) vs 10.7%(22/205) Upper respiratory infection: 3.4%(7/205) vs 5.4%(11/205) Weight gain: 2.9%(6/205) vs 22.4%(46/205)	Lamotrigine vs Olanzapine/Flouxetine: Withdrawals: 41.4%(85/205) vs 50.7%(104/205) Withdrawals due to adverse events: 13.7%(28/205) vs 18.0%(37/205)
Depression Olanzapine (Shelton RC et al., 2005) US & Canada	Fluoxetine vs Nortriptyline vs Olanzapine vs Olanzapine/Fluxetine: Akathisia: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Asthenia: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Cardiovascular effects: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Dyskinesia: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Headache: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Increased appetite: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Insomnia: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Nausea: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Nervousness: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Parkinsonian symptoms: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Somnolence: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Tremor: 2.1%(3/142) vs (NR/68) vs 4.9%(7/144) vs 11.6%(17/146) Weight gain: 0.0%(0/142) vs 0.0%(0/68) vs 4.3%(6/144) vs 7.8%(11/146)	Fluoxetine vs Nortriptyline vs Olanzapine vs Olanzapine/Fluxetine: Withdrawals: (NR/142) vs (NR/68) vs (NR/144) vs (NR/146) Withdrawals due to adverse events: 2.8%(4/142) vs 2.9%(2/68) vs 9.7%(14/144) vs 6.8%(10/146)

Condition, Drug **Author, Year** **Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
Tourettes Risperidone (Gilbert DL et al., 2004) US	Adverse events not reported before crossover.	Pimozide vs Pimozide vs Risperidone vs Risperidone: Withdrawals: 0.0%(0/7) vs 0.0%(0/7) vs 8.3%(1/12) vs 8.3%(1/12) Withdrawals due to adverse events: 0.0%(0/7) vs 0.0%(0/7) vs 0.0%(0/12) vs 0.0%(0/12)

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
ADL	Activities of Daily Life
AIAQ	Anger, Irritability, and Assault Questionnaire
ASI	Addiction Severity Index
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Index
BDHI	Buss-Durkee Hostility Index
BDI	Beck Depression Index
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelsen Melancholia Scale
CAPS	Clinician Administered PTSD Scale
CDSS	Calgary Depression Scale for Schizophrenia
CES-D	Center for Epidemiologic Studies Depression Scale
CGI	Clinical Global Impression Scale
CMAI	Cohen-Mansfield Agitation Inventory
CM-PNB	Cohen-Mansfield Physically Non-Aggressive Behavior
CPRS	Children's Psychiatric Rating Scale
CSDD	Cornell Scale for Depression in Dementia
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DCM	Dementia Care Mapping
DES	Dissociative Experiences Scale
DTS	Davidson Trauma Scale
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
FAST	Functional Assessment Staging Rating Scale
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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C3: Evidence Tables – Placebo Control Trials

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Autism Risperidone (McCracken JT et al., 2002) US RUPP Autism Study	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age 5-17, Weight ≥ 15 kg, Mental age ≥ 18 mos, Behavioral disturbances, CGI ≥ moderate severity, ABC Irritability subscale ≥ 18, Exclusion criteria: Medically significant disorders, DSM-IV Axis I disorder, not including primary condition studied, Psychotropic medication for behavioral disturbances	Placebo-2.4 mg/day average final dose Risperidone-1.8 mg/day average final dose Duration: 2.0 months	None 2-4 week washout period for all psychotropics
Autism Risperidone (Shea S et al., 2004) Canada RIS-CAN-23 Study	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: Healthy, Age 5-12, CARS ≥ 30 with or without mental retardation, DSM-IV Axis I diagnosis of PDD Exclusion criteria: Psychotic disorder, Medically significant disorders, Abnormal laboratory results, Seizure disorder, Allergic or toxic reactions to antipsychotic medications, Tardive dyskinesia, Neuroleptic malignant syndrome, Alcohol or substance abuse, Schizophrenia or other psychotic disorders, HIV, Risperidone used in last 3 mos, Previously unresponsive or intolerant to Risperidone	Placebo-dosage not reported Risperidone-1.48 mg/day average final dose Duration: 2.0 months	None None
Dementia and Agitation Olanzapine (De Deyn PP et al., 2004) Europe, Australia/NZ, South Africa F1D-MC-HGIV Study	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age ≥ 40, Hospitalized/ institutionalized, Psychosis/psychotic features, MMSE = 5-26 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied	Placebo-dosage not reported Olanzapine-1.0 mg/day fixed single dose Olanzapine-2.5 mg/day fixed single dose Olanzapine-5.0 mg/day fixed titration schedule Olanzapine-7.5 mg/day fixed titration schedule Duration: 2.5 months	14 wk of Placebo for randomization not described None

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/Randomization Method Wash-out period/Randomization Method**
Dementia and Agitation Olanzapine (Street JS et al., 2000) US HGEU Study	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: NPI/NH ≥ 3 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, MMSE > 24, Bedridden, Anticholinergic medications, Mood stabilizers, Antipsychotics other than the ones studied, Tricyclic antid	Placebo-dosage not reported Olanzapine-5 mg/day fixed single dose Olanzapine-10 mg/day fixed titration schedule Olanzapine-15 mg/day fixed titration schedule Duration: 1.5 months	3-14 dy of Placebo for non-placebo responders None
Dementia and Agitation Olanzapine & Risperidone (Ruths S et al., 2004) Western Europe	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: Nursing home resident, Age ≥ 65, Risperidone, olanzapine or haloperidol treatment ≥ 3 months, Resident ≥3 months before enrollment Exclusion criteria: Psychotic disorder, Mental retardation, Terminal illness, Recent major changes in health status	Continued tx w/ risperidone, olanzapine, or halperidol Withdrawal from risperidone, olanzapine, or halperidol Duration: 1.0 month	3-44 mo of Haloperidol, Risperidone, Olanzapine for patients who met study criteria None
Dementia and Agitation Quetiapine (Zhong X et al., 2004) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: NR Exclusion criteria: NR	Placebo-dosage not reported Quetiapine-100 mg/day fixed titration schedule Quetiapine-200 mg/day fixed titration schedule Duration: 2.5 months	None None
Dementia and Agitation Risperidone (Ballard CG et al., 2004) UK	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Neuroleptics ≥ 3 months (median prescription time > 1 yr), Age >65, Clinical Dementia Rating Scale ≥1 Exclusion criteria: NPI > 7	Placebo-dosage not reported Active tx (risperidone, thioridazine, haloperidol, chlorpromazine, or trifluoperazine Duration: 3.0 months	None None

Condition, Drug Author, Year Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/Randomization Method Wash-out period/Randomization Method**
Dementia and Agitation Risperidone (Brodaty H et al., 2003) Australia/New Zealand	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 55, FAST ≥ 4, MMSE ≤ 23, CMAI score of ≥ 4 on at least 1 aggressive item or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3, Nursing home resident, Resident ≥ 1 month prior to enrollment Exclusion criteria: Neurological or medical conditions diminishing cognitive function, Dementia other than primary condition, Major depressive disorder, Psychotic disorder, Tardive dyskinesia, Medically significant disorders, Abnormal laboratory results, Depot neuroleptic within 2 treatment cycles	Placebo-1.06 mg/day average final dose Risperidone-0.95 mg/day average final dose Duration: 3.0 months	None 7 dy of Psychotropics, Placebo for patients who completed the wash-out period
Dementia and Agitation Risperidone (Katz IR et al., 1999) US The Risperidone Study	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age ≥ 55, FAST ≥ 4, MMSE ≤ 23, BEHAVE-AD ≥ 8, BEHAVE-AD global rating ≥ 1 Exclusion criteria: Untreated reversible causes of dementia, Neurological or medical conditions diminishing cognitive function, HIV dementia, Substance induced dementia, Delirium, Amnestic disorder, Psychiatric diagnosis for psychotic disturbances	Placebo-dosage not reported Risperidone-0.5 mg/day in divided doses, Risperidone-1 mg/day fixed titration schedule in divided doses Risperidone-2 mg/day fixed titration schedule in divided doses Duration: 3.0 months	None 3-7 dy of Placebo for randomization not described
Dementia and Agitation Risperidone (Meguro K et al., 2004) Japan	Design: RCT Setting: Single center Jadad: 1	Inclusion criteria: Wandering behavior or aggressiveness > 4 in 7 consecutive days Exclusion criteria: Cerebrovascular disease, Parkinsons disease	Placebo-dosage not reported Risperidone- 1 mg/day fixed single dose Duration: 1.0 month	None None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Dementia and Agitation Risperidone (Mertens C, 1993) Western Europe	Design: CCT Setting: NR Jadad: 3	Inclusion criteria: Male or female, Age > 65, CDR = 1, 2, or 3 Exclusion criteria: Neurological or medical conditions diminishing cognitive function, Neurologic disorder, not including primary conditioned studied, Psychiatric disorder, not including primary conditioned studied	Placebo Risperidone-2 mg/day average final dose Duration: 0.9 month	1 wk of Placebo for randomization not described None
Depression Olanzapine (Howanitz E et al., 2001) NR	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: NR Exclusion criteria: NR	Placebo-dosage not reported Olanzapine-6.25 mg/day average final dose Duration: 1.5 months	None None
Depression Olanzapine (Kinrys G et al., 2002) US	Design: RCT Setting: NR Jadad: 3	Inclusion criteria: HAM-A = 50% reduction, CGI ≥ 4 Exclusion criteria: NR	Placebo-dosage not reported Olanzapine-9.4 mg/day average final dose Duration: 1.5 months	6 wk of Fluoxetine for symptomatic patients None
Depression Olanzapine (Rothschild AJ et al., 2004) (Corya S et al., 2002) US The HGGA Study	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age ≥ 18, HAM-D ≥ 20 Exclusion criteria: Psychotic disorder, Pregnant, Lactating	Placebo-dosage not reported Olanzapine-11.9 mg/day average final dose Olanzapine-12.4 mg/day average final dose, Fluoxetine- 23.5 mg/day average final dose Duration: 2.0 months	None None
Depression Olanzapine (Shi L et al., 2004) US, Australia/NZ, Europe, Colombia	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 18, MADRS ≥ 20, At least 1 manic or mixed episode requiring treatment with mood stabilizer or antipsychotic Exclusion criteria: Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders	Placebo-dosage not reported Olanzapine-9.7 mg/day average final dose Olanzapine-7.4 mg/day average final dose, Fluoxetine- 25 or 50 mg Duration: 2.0 months	None 2-14 dy of Psychotropics, except benzodiazepines or anticholinergics for patients who completed the wash-out period

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Depression Olanzapine (Tohen M et al., 2003) US, Australia/NZ, Europe, Colombia	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age ≥ 18, MADRS ≥ 20, At least 1 manic or mixed episode requiring treatment with mood stabilizer or antipsychotic Exclusion criteria: Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders	Placebo-dosage not reported Olanzapine-9.7 mg/day average final dose Olanzapine-7.4 mg/day average final dose, Fluoxetine- 39.3 mg/day average final dose Duration: 2.0 months	None 2-14 dy of Psychotropics, except benzodiazepines or anticholinergics for patients who completed the wash-out period
Depression Olanzapine (Tohen M et al., 2000) US The Olanzapine HGGW Study	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: YMRS ≥ 20 Exclusion criteria: Medically significant disorders, Alcohol or substance abuse or dependency, Suicidal or violent	Placebo-dosage not reported Olanzapine-16.4 mg/day average final dose Duration: 1.0 month	None 997 dy of Psychotropics for randomization not described
Depression Olanzapine (Tohen M et al., 1999) US The Olanzapine HGEH Study	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age 18-65, YMRS ≥ 20 Exclusion criteria: Medically significant disorders, Alcohol or substance abuse or dependency, Suicidal or violent	Placebo-dosage not reported Olanzapine-14.9 mg/day average final dose Duration: 0.8 month	None 2-4 dy of All medications except benzodiazepines for randomization not described
Depression Olanzapine (Tohen M et al., 2003) US	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: YMRS ≤ 12, HAM-21 ≤ 8 Exclusion criteria: NR	Placebo-dosage not reported Olanzapine-5-20 mg/day ' Duration: 13.0 months	None None
Depression Olanzapine (Tollefson GD et al., 1999) US Collaborative Crossover Study	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 18, Clozapine treatment within 4 wks Exclusion criteria: Alcohol or substance abuse or dependency, Suicidal or violent, Previous exposure to study drug, Medically significant disorders	Placebo-dosage not reported Olanzapine-10 mg/day fixed single dose Duration: 0.2 month	None None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Dementia-Agitation Olanzapine & Risperidone (van Reekum R et al., 2002) Canada	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: Hospitalized/institutionalized, Antipsychotic treatment ≥ 6 months Exclusion criteria: Schizophrenia, Delirium, Resistant to antipsychotic treatment, Antipsychotic use for nausea, BEHAVE-AD ≥ 3 at screening, 1 week before study, or within 2 weeks pretrial period	Withdrawal from risperidone, olanzapine, halperidol, thiroidazine, or loxapine Continued tx w/ risperidone, olanzapine, halperidol, thiroidazine, or loxapine Duration: 6.0 months	1.5-1.8 yr of Risperidone, Olanzapine, Haloperidol, Anticonvulsants for patients who met study criteria None
Depression Quetiapine (Calabrese J et al., 2004) US	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: HAM-D ≥ 20, YMRS ≤ 12 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied	Placebo-dosage not reported Quetiapine-300 mg/day fixed titration schedule Quetiapine-600 mg/day fixed titration schedule Duration: 2.0 months	None None
Dementia and Agitation Risperidone (Mintzer J et al., 2004) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: MMSE = 5-23, Age ≥ 55, BEHAVE-AD Psychosis Subscale ≥ 2, Able to ambulate, walk with assistance or use wheelchair independently Exclusion criteria: Medically significant disorders, Abnormal laboratory results, Epilepsy, Neurological or medical conditions diminishing cognitive function or that cause psychosis, Cancer, except for non-melanoma of the skin, Recent depot neuroleptic injections, Change in medications in preceding 30 dys	Placebo-53.1 mg mean modal dose Risperidone-1.2 mg mean modal dose Duration: 2.0 months	None 7 dys of Psychotropics for randomization not described
Depression Risperidone (Gharabawi GM et al., 2004) International ARISe-RD Study	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Age 18-85, HAM-D ≤ 7, CGI score = 1 or 2, Achieved symptomatic remission following ≥ wks of RIS augmentation Exclusion criteria: Pregnant, lactating, psychiatric history, DSM-IV diagnosis confounded by various things, including being medically unstable, testing positive on urine drug screen, impaired hepatic or renal function, history failure of citalopram or any antidepressant with risperidone augmentation, etc.	Citalopram-mean modal dose 53.1 mg/day + Placebo Citalopram-53.1 mg/day + Risperidone-1.2 mg/day mean modal dose Duration: 6.0 months	4-6 wk of Citalopram monotherapy, then Risperidone augmentation 4-6 wk in citalopram non-responders None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Depression Ziprasidone (Daniels DG et al., 1999) US & Canada The Ziprasidone Study	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 18, Hospitalized/institutionalized, PANSS ≥ 60, PANSS with score ≥ 4 on at least 2 items on positive symptoms subscale, CGI ≥ 3, Exclusion criteria: Resistant to antipsychotic treatment, Hospitalized > 4 weeks, Alcohol or substance abuse or dependency, Mental retardation, Organic mental disorder, Brief reactive psychosis, Depot neuroleptic within 4 weeks, Suicidal or violent	Placebo-dosage not reported Ziprasidone-80 mg/day fixed single dose Ziprasidone-160 mg/day fixed titration schedule Duration: 1.5 months	None 3 dy of Neuroleptics, Antidepressants, Sedatives, Anxiolytics, Hypnotics, Anticholinergics, Beta-adrenoceptor antagonists for patients who completed the wash-out period
Depression Ziprasidone (Keck P Jr et al., 1998) US The Ziprasidone Study	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Age 18-64, Hospitalized/institutionalized, 1 year duration primary condition, BPRS ≥ 37, BPRS ≥ 4 on 2 or more of core items, Exclusion criteria: Nursing home/residential center resident, Resistant to antipsychotic treatment, Alcohol or substance abuse or dependency, Residual schizophrenia, Mental retardation, Organic mental disorder, Brief reactive psychosis, Suicidal or violent	Placebo-dosage not reported Ziprasidone-40 mg/day fixed single dose Ziprasidone-120 mg/day fixed single dose Duration: 1.0 month	None 4-7 dy of Placebo, Antidepressants, Anticholinergics, Thymoleptics, Anxiolytics, Hypnotics for patients who completed the wash-out period
Depression and PTSD Risperidone (Bartzokis G et al., 2004) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Proof of military service, CAPS ≥ 65 Exclusion criteria: Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders, Neurological or medical conditions diminishing cognitive function, Antipsychotic medications, Seizure disorder or epilepsy or risk, Change in antidepressant regimen within 6 wks prior to study entry	Placebo-dosage not reported Risperidone-3 mg/day average final dose Duration: 4.0 months	None None
PTSD Risperidone (Padala PR et al., 2005) US	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: Level of understanding to perform all tests and examinations Exclusion criteria: Bipolar disorder, Schizophrenia, Medically significant disorders, Abnormal laboratory results, Suicidal or violent, Alcohol or substance abuse or dependency, Previous exposure to study drug, Antipsychotics other than the ones studied, Previous exposure to risperidone, Pregnancy/nursing, Use of psychotropics	Placebo-dosage not reported Risperidone-2.62 mg/day average final dose Duration: 3.0 months	None 2 wk of Psychotropics for randomization not described

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
PTSD Risperidone (Reich DB et al., 2004) US	Design: RCT Setting: Single Center Jadad: 2	Inclusion criteria: Understand English, Able to give informed consent, Level of understanding to perform all tests and examinations, CAPS-1 ≥ 50, PTSD related to childhood physical, sexual, emotional or verbal abuse, Exclusion criteria: Medically significant disorders, Alcohol or substance abuse or dependency, Psychotic disorder, Organic mental disorder, Antipsychotics other than the ones studied, Mood stabilizers, Risperidone treatment of 1 week or more, Suicidal or violent, Pregnancy/nursing, Entry into individual psychotherapy within 3 mos of study, and entry into group therapy within 1 mo of study	Placebo-dosage not reported Risperidone-1.41 mg/day average final dose Duration: 2.0 months	None None
OCD Olanzapine (Bystritsky A et al., 2004) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Age 18-65 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, DSM-IV Axis II disorder, not including primary condition studied, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, Pregnant, Medically significant disorders, HAM-D > 20, Bizarre psychosis	Placebo-16.9 mg/day average final dose Olanzapine-11.2 mg/day average final dose Duration: 1.5 months	None None
OCD Risperidone (Buchsbaum MS, 2003) NR	Design: CCT Setting: NR Jadad: 1	Inclusion criteria: Refractory to SRI therapy Exclusion criteria: NR	Placebo-dosage not reported Risperidone-dosage not reported Duration: 2.0 months	None None
OCD Risperidone (Erzegovesi S et al., 2005) Western Europe	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: Age 18-65, 1 year duration primary condition, Drug-free within 3 weeks, Drug-free for at least 3 wks prior to study entry Exclusion criteria: Antiobsessional medications, Psychiatric disorders except for panic disorder and tic disorders, Pregnant, Lactating, Seizure disorder or epilepsy or risk, Medical conditions contraindicating use of fluvoxamine, Contraindication to risperidone	Placebo-dosage not reported Risperidone-0.5 mg/day fixed single dose Duration: 1.5 months	12 wk of Fluvoxamine for responders separated from non-responders None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
OCD Risperidone (Hollander E et al., 2003) US	Design: RCT Setting: NR Jadad: 4	Inclusion criteria: CGI ≥ 3, SRI therapy ≥ 12 weeks, ≥2 SRI trials of adequate dose and duration Exclusion criteria: Medically significant disorders, Schizophrenia and schizoaffective disorder, Bipolar disorder	Placebo-2.75 mg/day average final dose Risperidone-2.25 mg/day average final dose Duration: 2.0 months	None None
PTSD Olanzapine (Butterfield MI et al., 2001) US	Design: RCT Setting: NR Jadad: 3	Inclusion criteria: Age 18-70, Understand English, Able to give informed consent Exclusion criteria: Bipolar disorder, Psychotic disorder, Mental retardation, Alcohol or substance abuse or dependency, Suicidal or violent	Placebo-13.9 mg/day average final dose Olanzapine-14.1 mg/day average final dose Duration: 2.5 months	None None
PTSD Olanzapine (Stein MB et al., 2002) US	Design: RCT Setting: VA Healthcare S Jadad: 3	Inclusion criteria: Refractory to SRI therapy Exclusion criteria: NR	Placebo-20.00 mg/day average final dose Olanzapine-15.00 mg/day average final dose Duration: 2.0 months	Variable weeks of SSRIs for patients minimally responsive to SSRIs None
PTSD Risperidone (Hamner MB et al., 2003) US	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: Age ≥ 18, Psychosis/psychotic features, PANSS ≥ 60, PANSS with score ≥ 4 on at least 1 item on positive symptoms subscale, Exclusion criteria: Toxic reactions to antipsychotic medications, Medically significant disorders, Alcohol or substance abuse or dependency, Schizophrenia, Bipolar disorder, Suicidal or violent, Risperidone hypersensitivity	Placebo-dosage not reported Risperidone-2.5 mg/day average final dose Duration: 1.3 months	1 wk of Placebo for non-placebo responders Prior to run-in antipsychotics or thymoleptics (carbamazepine, valproic acid and lithium) had medications reduced or discontinued
PTSD Risperidone (Monnelly EP et al., 2003) US	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: PCL-M ≥ 20 on cluster D subscale Exclusion criteria: Schizophrenia, Bipolar disorder with psychotic features, Organic mental disorder, Antipsychotic medications, Alcohol/substance dependency in remission	Placebo-0.62 mg/day average final dose Risperidone-0.57 mg/day average final dose Duration: 1.5 months	None None
Personality Disorder Olanzapine (Bogenschutz MP et al., 2004) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Age 18-60 Exclusion criteria: Psychotropic medications, Pregnant, Bipolar disorder, Psychotic disorder, Major depressive disorder, Alcohol or substance abuse or dependency, Suicidal or violent, Neurological disorder	Placebo-10.2 mg/day average final dose Olanzapine-6.9 mg/day average final dose Duration: 3.0 months	None None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Personality Disorder Olanzapine (Zanarini MC et al., 2001) US	Design: RCT Setting: NR Jadad: 5	Inclusion criteria: Age 18-40 Exclusion criteria: Previous exposure to study drug, Medically significant disorders, Seizure disorder or epilepsy or risk, Psychotropic medications, Alcohol or substance abuse or dependency, Suicidal or violent, Pregnant, Lactating	Placebo-dosage not reported Olanzapine-5.33 mg/day average final dose Duration: 6.0 months	None None
Personality Disorder Risperidone (Koenigsberg HW et al., 2003) US	Design: RCT Setting: Multi-center Jadad: 4	Inclusion criteria: Healthy, Age 18-60 Exclusion criteria: Alcohol or substance abuse or dependency, Use psychotropic medications within 2 wks	Placebo-dosage not reported Risperidone-0.25-2 mg/day flexible dose Duration: 2.3 months	2 wk of Placebo for randomization not described None
Tourettes Ziprasidone (Sallee FR et al., 2000) US	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age 7-17, Severe tic symptoms requiring medication treatment, Healthy, Free of psychotropic medications within 4 weeks Exclusion criteria: Abnormal laboratory results, Neuroleptic malignant syndrome, Atypical antipsychotics sensitivity, Major depressive disorder, Pervasive developmental disorder, Autism, Mental retardation, Eating disorders	Placebo-dosage not reported Ziprasidone-28.2 mg/day average final dose Duration: 1.8 months	None None
Dementia and Agitation Aripiprazole (Breder C et al., 2004) NR	Design: RCT Setting: Multi-center Jadad: 1	Inclusion criteria: Psychosis/psychotic features, Nursing home resident, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items, Age 55-95, MMSE = 6-22 Exclusion criteria: NR	Placebo - dosage not reported Aripiprazole - 2 mg/day fixed single dose Aripiprazole - 5 mg/day fixed single dose Aripiprazole - 10 mg/day fixed titration schedule Duration: 2.5 months	None ≥ 7 dy of psychotropics for patients who completed the wash-out period

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Dementia and Agitation Aripiprazole (De Deyn P et al., 2005) NR	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items, Age 55-95, Noninstitutionalized, Delusions or hallucinations ≥ 1 month, MMSE = 6-24 Exclusion criteria: Bipolar disorder, Schizophrenia, Delirium, Amnestic disorder, Schizoaffective disorder, Mood disorders with psychotic features, Psychotic features accounted better by disease other than the one studied or by effects of a substance, Refractory to neuroleptics	Placebo - dosage not reported Aripiprazole - 10 mg/day average final dose Duration: 2.5 months	None 7 wk of psychotropics for patients who completed the wash-out period
Dementia and Agitation Aripiprazole (Streim JE et al., 2004) US	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: Delusions or hallucinations ≥ 1 month, Nursing home resident, Age 55-95, MMSE = 6-22, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items Exclusion criteria: NR	Placebo - dosage not reported Aripiprazole - 8.6 mg/day average final dose Duration: 2.5 months	None None
Depression Aripiprazole (McQuade R et al., 2004) NR	Design: RCT Setting: NR Jadad: 2	Inclusion criteria: Recent manic episode, but did not participate in a trial of study drug, Recently completed trial of study drug, YMRS ≤ 10, MADRS ≤ 13 Exclusion criteria: NR	Placebo - dosage not reported Aripiprazole - 24.3 mg/day average final dose Duration: 6.5 months	6-18 wk of Aripiprazole for randomization not described None
Depression Olanzapine (Kennedy J et al., 2005) US	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Age ≥ 40 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, Neurologic disorder, not including primary conditioned studied, NPI > 1 on delusions, hallucinations, agitation/aggression or dysphoria items, Score ≥ 1 on cholinesterase inhibitor use, antioxidant or herbal supplement items ≤ 4 week	Placebo - dosage not reported Olanzapine - 2.5-7.5 mg/day flexible dose Duration: 6.5 months	None 10-18 dy of medications to treat Alzheimers for randomization not described
Depression and Personality Disorder Olanzapine (Soler J et al., 2005) Western Europe	Design: RCT Setting: Single center Jadad: 2	Inclusion criteria: CGI ≥ 4, Age 18-45 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, Psychotherapy, Sexually active females of child bearing age not using an effective contraceptive method	Placebo - dosage not reported Olanzapine - 883 mg/day average final dose Duration: 3.0 months	None None

Condition, Drug Author, Year Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/Randomization Method Wash-out period/Randomization Method
Tourettes Risperidone (Scahill L et al., 2003) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Age 7-65 Exclusion criteria: Major depressive disorder, Psychosis/psychotic features, Anxiety disorder, Wechsler Intelligence Scale age approximate IQ < 70, Previous adequate trial of risperidone, Medically significant disorders, Y-BOCS or CY-BOCS > 15, Psychotropic medications	Placebo - 3.3 mg/day fixed titration schedule Risperidone - 2.5 mg/day fixed titration schedule Duration: 2.0 months	None 7-14 wk of placebo for patients who completed the wash-out period

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**
Autism Risperidone (McCracken JT et al., 2002) US RUPP Autism Study	Anticonvulsant agent for seizure control if no dose change in 4 wks and no seizures for at least 6 mos.	Assessed at baseline and 8 weeks: ABC, CGI	9/5-17 81% male Caucasian, African-American, Hispanic, Asian, NOS	270/101/ 101
Autism Risperidone (Shea S et al., 2004) Canada RIS-CAN-23 Study	Anticholinergic medications, Anti-asthmatics, A single anticonvulsant and medications for sleep or anxiety if doses of each had been stable for at least 30 days	Assessed at baseline and 8 weeks: ABC, N-CBRF, CGI, VAS	7.5 77% male Caucasian, African-American, NOS	NR/80/79
Dementia and Agitation Olanzapine (De Deyn PP et al., 2004) Europe, Australia/NZ, South Africa F1D-MC-HGIV Study	Benzodiazepines, Sedative/ hypnotics	Assessed at baseline and 10 weeks: NPI-NH, CGI, BPRS, MMSE, SIB	77/NR 25% male Caucasian, NOS	NR/652/ NR
Dementia and Agitation Olanzapine (Street JS et al., 2000) US HGEU Study	Benzodiazepines	Assessed at baseline and 6 weeks: NPI-NH, BPRS, MMSE	83/61-97 39% male Caucasian, African-American, Hispanic, NOS	288/206/ 206
Dementia and Agitation Olanzapine & Risperidone (Ruths S et al., 2004) Western Europe	Antidepressants, sedative/ Hypnotic, Anxiolytics, Anticholinergic medications, Narcotic analgesics	Assessed at baseline and 4 weeks: NPI-Q, Sleep disorders	83/NR 20% male NR	51/30/30
Dementia and Agitation Quetiapine (Zhong X et al., 2004) US	NR	Assessed at baseline and 10 weeks: PANSS, CGI	83/NR NR NR	NR/333/ NR
Dementia and Agitation Risperidone (Ballard CG et al., 2004) UK	NR	Assessed at baseline and 3 months: NPI, DCM	83/NR 19% male NR	NR/100/ 100

Condition, Drug **Author, Year** **Country, Trial named**	**Allowed other medications**	**Method of outcome assessment** **Timing of assessment**	**Age mean/** **Age range** **Gender** **Ethnicity**	**Screened/** **Eligible/** **Enrolled**
Dementia and Agitation Risperidone (Brodaty H et al., 2003) Australia/New Zealand	Anti-EPS medications, Benzodiazepines, Tricyclic antidepressants, anticholinergic medications, short-acting sedative/hypnotic agents, and narcotic analgesics	Assessed at baseline and 12 weeks: CMAI, BEHAVE-AD, FAST, MMSE, CGI	83/NR 28% male NR	384/345/ 345
Dementia and Agitation Risperidone (Katz IR et al., 1999) US The Risperidone Study	Benztropine, lorzepam, chloral hydrate	Assessed at baseline and 12 weeks: BEHAVE-AD, CMAI, CGI, MMSE	83/NR 32% male Caucasian, NOS	729/625/ 625
Dementia and Agitation Risperidone (Meguro K et al., 2004) Japan	Acetyl- cholinesterase inhibitors	Assessed at baseline and 1 months: Sleep disorders, Wandering behavior	78/68-90 21% male NR	NR/34/34
Dementia and Agitation Risperidone (Mertens C, 1993) Western Europe	NR	Assessed at baseline and 4 weeks: BEHAVE-AD, CGI, MMSE, VAS, ADL	NR/65-88 31% male NR	NR/39/39
Depression Olanzapine (Howanitz E et al., 2001) NR	NR	Assessed at baseline and 6 weeks: NPI, BPRS, ADAS-cog	73/NR NR NR	NR/16/16
Depression Olanzapine (Kinrys G et al., 2002) US	Fluoxetine	Assessed at baseline and 6 weeks: HAM_D_HDRS, HAM_A, CGI	NR/NR NR NR	NR/14/14
Depression Olanzapine (Rothschild AJ et al., 2004) (Corya S et al., 2002) US The HGGA Study	NR	Assessed at baseline and 8 weeks: HAM_D_HDRS, HAM_A, BPRS, CGI	41/NR 48% male Caucasian, NOS	NR/124/ 124

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**
Depression Olanzapine (Shi L et al., 2004) US, Australia/NZ, Europe, Colombia	Benzodiazepines	Assessed at baseline and 8 weeks: SF-36, QLDS	40/NR 35% male Caucasian, NOS	1072/833/833
Depression Olanzapine (Tohen M et al., 2003) US, Australia/NZ, Europe, Colombia	Benzodiazepines	Assessed at baseline and 8 weeks: MADRS, HAM_A, CGI, YMRS	42/NR 37% male Caucasian, NOS	1072/833/833
Depression Olanzapine (Tohen M et al., 2000) US The Olanzapine HGGW Study	Benzodiazepines	Assessed at baseline and 4 weeks: YMRS, HAM_D_HDRS, CGI, PANSS	39/NR 50% male Caucasian, NOS	NR/115/ 115
Depression Olanzapine (Tohen M et al., 1999) US The Olanzapine HGEH Study	Anticholinergic medications, Benzodiazepines	Assessed at baseline and 3 weeks: YMRS, HAM_D_HDRS, PANSS, CGI, SF-36	40/NR 52% male Caucasian, NOS	NR/139/ 139
Depression Olanzapine (Tohen M et al., 2003) US	NR	Assessed at baseline and 52 weeks: HAM_D_HDRS, YMRS	NR/NR NR NR	NR/361/ 361
Depression Olanzapine (Tollefson GD et al., 1999) US Collaborative Crossover Study	Anti-EPS medications, Benzodiazepines, Clozapine	Assessed at baseline and 997 day: CGI, PANSS, BPRS, MADRS, MMSE	39/NR 71% male Caucasian, African-American, Hispanic	115/106/ 106
Dementia-Agitation Olanzapine & Risperidone (van Reekum R et al., 2002) Canada	Lorazepam if needed	Assessed at baseline and 6 months: BEHAVE-AD, NPI, ROAS, MMSE, MDRS, BDS, CGI	84/NR 50% male NR	NR/34/34

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**
Depression Quetiapine (Calabrese J et al., 2004) US	NR	Assessed at baseline and 8 weeks: HAM_D_HDRS, MADRS, Q-LES-Q, CGI, Sleep disorders	37/NR 43% male NR	832/542/542
Dementia and Agitation Risperidone (Mintzer J et al., 2004) US	Lorazepam permitted	Assessed at baseline and 8 weeks: BEHAVE-AD, CGI	83/NR 23% male Caucasian, African-American, Hispanic, Asian, NOS	NR/473/ 473
Depression Risperidone (Gharabawi GM et al., 2004) International ARISe-RD Study	Zolpidem, lorazepam, zopiclone, zaleplon, benztropine	Assessed at baseline and 24 weeks: CGI, HAM_D_HDRS	48/NR 36% male Caucasian, NOS	489/241/ 241
Depression Ziprasidone (Daniels DG et al., 1999) US & Canada The Ziprasidone Study	Lorazepam	Assessed at baseline and 6 weeks: PANSS, CGI, BPRS, MADRS	37/18-67 71% male Caucasian, African-American, Asian, NOS	440/302/302
Depression Ziprasidone (Keck P Jr et al., 1998) US The Ziprasidone Study	Anti-EPS medications, Beta-blockers, Lorazepam	Assessed at baseline and 4 weeks: BPRS, CGI, SANS	39/19-76 79% male Caucasian, African-American, Asian, NOS	203/139/139
Depression and PTSD Risperidone (Bartzokis G et al., 2004) US	Antidepressants, Anxiolytics, Sedative/hypnotics	Assessed at baseline and 16 weeks: HAM_D_HDRS, HAM_A, PANSS, CAPS	52/38-63 100% male Caucasian, African-American, Asian, Native American	73/65/65

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**
PTSD Risperidone (Padala PR et al., 2005) US	Diphenhydramine 25-50 mg/dy PRN	Assessed at baseline and 10 weeks: TOP8, HAM_A, CAPS, CGI, HAM_D_HDRS	41/NR 0% male Caucasian, African-American, NOS	NR/20/20
PTSD Risperidone (Reich DB et al., 2004) US	Antidepressants, Benzodiazepines permitted	Assessed at baseline and 8 weeks: CAPS	27/NR 0% male Caucasian, African-American, Asian	NR/21/21
OCD Olanzapine (Bystritsky A et al., 2004) US	SRIs	Assessed at baseline and 6 weeks: YBOCS, HAM_D_HDRS, HAM_A, CGI	41/18-65 50% male NR	NR/26/26
OCD Risperidone (Buchsbaum MS, 2003) NR	NR	Assessed at baseline and 8 weeks: CGI .	NR/NR NR NR	NR/16/16
OCD Risperidone (Erzegovesi S et al., 2005) Western Europe	Fluvoxamine, Previously established benzodiazepines used as hypnotics	Assessed at baseline and 6 weeks: YBOCS, NIMH-OC, HAM_D_HDRS, CGI	37/NR 53% male NR	NR/45/45
OCD Risperidone (Hollander E et al., 2003) US	SRIs	Assessed at baseline and 8 weeks: YBOCS, HAM_D_HDRS, CGI	39/NR 56% male NR	NR/16/16
PTSD Olanzapine (Butterfield MI et al., 2001) US	NR	Assessed at baseline and 10 weeks: SIP, SPRINT, TOP8, DTS, SDS, CGI	43/26-73 7% male Caucasian, African-American	NR/15/15

Condition, Drug Author, Year Country, Trial named	Allowed other medications	Method of outcome assessment Timing of assessment	Age mean/ Age range Gender Ethnicity	Screened/ Eligible/ Enrolled
PTSD Olanzapine (Stein MB et al., 2002) US	SRIs	Assessed at baseline and 8 weeks: CAPS, CES-D, Pittsburg Sleep, CGI	53/34-69 100% male NR	NR/21/19
PTSD Risperidone (Hamner MB et al., 2003) US	Antidepressants, Benzodiazepines, Chloral hydrate, Mood stabilizers	Assessed at baseline and 5 weeks: PANSS, CAPS	52/47-68 100% male Caucasian, African-American	NR/40/40
PTSD Risperidone (Monnelly EP et al., 2003) US	Antidepressants, Benzodiazepines, Buspirone, Mood stabilizers	Assessed at baseline and 6 weeks: OAS-M, PCL-M, BDHI, STAT-T, STAS-AX, BDI, BAI, DES, STAT-S	51/NR 100% male Caucasian, African-American, Hispanic	NR/16/16
Personality Disorder Olanzapine (Bogenschutz MP et al., 2004) US	NR	Assessed at baseline and 12 weeks: CGI, OAS-M, AIAQ, HAM_D_HDRS, HAM_A, SCL_90, ASI	33/18-54 38% male Caucasian, Hispanic, Asian, NOS	NR/40/40
Personality Disorder Olanzapine (Zanarini MC et al., 2001) US	NR	Assessed at baseline and 24 weeks: SCL_90, HAM_D_HDRS, DES, PANSS, GAF	27/NR 0% male Caucasian, NOS	30/28/28
Personality Disorder Risperidone (Koenigsberg HW et al., 2003) US	NR	Assessed at baseline and 9 weeks: PANSS, HAM_D_HDRS, CGI, SPQ	41/NR 83% male Caucasian, African-American, Hispanic	NR/25/25
Tourettes Ziprasidone (Sallee FR et al., 2000) US	NR	Assessed at baseline and 56 day: Yale Global Tic, CGI, Goetz Videotaping Scale, CY-BOCS	12/7-16 79% male NR	29/28/28

Condition, Drug Author, Year Country, Trial named	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**	**Screened/ Eligible/ Enrolled**
Dementia and Agitation Aripiprazole (Breder C et al., 2004) NR	Antidepressants, Cognition enhancers at stable doses, zolpidem, lorazepam as long as it was not within 12 hours of baseline and double-blind study evaluations	Assessed at baseline and 10 weeks: BPRS, NPI-NH, CGI, CMAI, Extrapyramidel side effects	83 / 56-97 21% male NR	NR/487/487
Dementia and Agitation Aripiprazole (De Deyn P et al., 2005) NR	Sedative/hypnotics, Acetylcholinesterase inhibitors, Rivastigmine, Tacrine, Antidepressants, Benztropine	Assessed at baseline and 10 weeks: NPI, BPRS, CGI, MMSE, Extrapyramidel side effects	82 / NR 28% male Caucasian, NOS	NR/208/208
Dementia and Agitation Aripiprazole (Streim JE et al., 2004) US	Antidepressants, Cognition enhancers at stable doses, zolpidem, lorazepam	Assessed at baseline and 10 weeks: BPRS, CGI, NPI-NH, CMAI, CSDD, Extrapyramidel side effects	83 / 59-96 24% male NR	NR/256/256
Depression Aripiprazole (McQuade R et al., 2004) NR	Not reported	Assessed at baseline and 26 weeks: YMRS, MADRS, Extrapyramidel side effects	NR / NR NR NR	567/161/161
Depression Olanzapine (Kennedy J et al., 2005) US	Benzodiazepines, Hypnotics	Assessed at baseline and 26 weeks: NPI, MMSE, ADAS-cog, Extrapyramidel side effects, CIBIC	78 / NR 44% male Caucasian, NOS	446/268/268
Depression and Personality Disorder Olanzapine (Soler J et al., 2005) Western Europe	Antidepressants, Mood stabilizers, Benzodiazepines	Assessed at baseline and 12 weeks: HAM_D_HDRS, HAM_A, CGI, Dysfunctional behaviors	27 / NR 13% male NR	125/60/60
Tourettes Risperidone (Scahill L et al., 2003) US	Not reported	Assessed at baseline and 8 weeks: Yale Global Tic, TSSR, CGI, Extrapyramidel side effects	20 / 6-62 88% male NR	49/34/34

Condition, Drug Author, Year Country, Trial named	**Withdrawn/Lost to FU/ Analyzed**	**Results**	**Method of adverse events assessment**
Autism Risperidone (McCracken JT et al., 2002) US RUPP Autism Study	18/3/101	Autism-Change in ABC-I at 8 weeks: Placebo vs Risperidone-SMD = -1.24(-1.667, -0.814)	Monitored, elicited by investigator
Autism Risperidone (Shea S et al., 2004) Canada RIS-CAN-23 Study	7/0/79	Autism-Change in ABC-I at 8 weeks: Placebo vs Risperidone-SMD = -0.932(-1.403, -0.461)	Monitored

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Dementia and Agitation Olanzapine (De Deyn PP et al., 2004) Europe, Australia/NZ, South Africa F1D-MC-HGIV Study	NR/NR/ NR	Dementia_agitation-Change in NPI-NH (agitation) at 10 weeks: Placebo vs Olanzapine 1 mg/d-SMD = -0.142(-0.387,0.103) Dementia_agitation-Change in NPI-NH (agitation) at 10 weeks: Placebo vs Olanzapine 2.5 mg/d-SMD = -0.114 (-0.356,0.128) Dementia_agitation-Change in NPI-NH (agitation) at 10 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.114(-0.361,0.134) Dementia_agitation-Change in NPI-NH (agitation) at 10 weeks: Placebo vs Olanzapine 7.5mg/d-SMD = -0.142(-0.387,0.103) Dementia_global-Change in NPI-NH (total) at 10 weeks: Placebo vs Olanzapine 1 mg/d-SMD = 0.042(-0.203,0.287) Dementia_global-Change in NPI-NH (total) at 10 weeks: Placebo vs Olanzapine 2.5 mg/d-SMD = -0.047 (-0.289,0.194) Dementia_global-Change in NPI-NH (total) at 10 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.053(-0.3,0.194) Dementia_global-Change in NPI-NH (total) at 10 weeks: Placebo vs Olanzapine 7.5mg/d-SMD = -0.1(-0.345,0.145) Dementia_psychosis-Change in NPI-NH (psychosis) at 10 weeks: Placebo vs Olanzapine 1 mg/d-SMD = -0.12(-0.365,0.124) Dementia_psychosis-Change in NPI-NH (psychosis) at 10 weeks: Placebo vs Olanzapine 2.5 mg/d-SMD = -0.281(-0.524, -0.038) Dementia_psychosis-Change in NPI-NH (psychosis) at 10 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.12(-0.368,0.127) Dementia_psychosis-Change in NPI-NH (psychosis) at 10 weeks: Placebo vs Olanzapine 7.5mg/d-SMD = -0.261(-0.506, -0.015)	Monitored, reported by patient

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Dementia and Agitation Olanzapine (Street JS et al., 2000) US HGEU Study	54/0/152	Dementia_agitation-Change in NPI-NH (agitation) at 6 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.284(-0.68,0.112) Dementia_agitation-Change in NPI-NH (agitation) at 6 weeks: Placebo vs Olanzapine 10 mg/d-SMD = -0.227(-0.633,0.179) Dementia_agitation-Change in NPI-NH (agitation) at 6 weeks: Placebo vs Olanzapine 15 mg/d-SMD = -0.142(-0.542,0.258) Dementia_global-Change in NPI-NH (total) at 6 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.463(-0.862,-0.063) Dementia_global-Change in NPI-NH (total) at 6 weeks: Placebo vs Olanzapine 10 mg/d-SMD = -0.447(-0.857, -0.037) Dementia_global-Change in NPI-NH (total) at 6 weeks: Placebo vs Olanzapine 15 mg/d-SMD = -0.131(-0.531,0.268) Dementia_psychosis-Change in NPI-NH (psychosis) at 6 weeks: Placebo vs Olanzapine 5 mg/d-SMD = -0.642(-1.046,-0.238) Dementia_psychosis-Change in NPI-NH (psychosis) at 6 weeks: Placebo vs Olanzapine 10 mg/d-SMD = -0.441(-0.851, -0.032) Dementia_psychosis-Change in NPI-NH (psychosis) at 6 weeks: Placebo vs Olanzapine 15 mg/d-SMD = -0.301(-0.702,0.1)	Monitored
Dementia and Agitation Olanzapine & Risperidone (Ruths S et al., 2004) Western Europe	0/0/30	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of follow-ups.	Monitored
Dementia and Agitation Quetiapine (Zhong X et al., 2004) US	NR/NR/NR	Insufficient statistics for effect-size calculation.	Monitored
Dementia and Agitation Risperidone (Ballard CG et al., 2004) UK	28/0/NR	Not a comparison of interest for statistical analysis.	Monitored, elicited by investigator

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Dementia and Agitation Risperidone (Brodaty H et al., 2003) Australia/New Zealand	101/0/236	Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Placebo vs Risperidone-SMD = -0.538(-0.768, -0.308) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Placebo vs Risperidone-SMD = -0.421(-0.682, -0.160)	Monitored, reported by patient, clinical examination
Dementia and Agitation Risperidone (Katz IR et al., 1999) US The Risperidone Study	190/0/435	Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Placebo vs Risperidone 0.5mg/d-SMD = -0.351(-0.609, -0.093) Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Placebo vs Risperidone 1 mg/d-SMD = -0.602(-0.872,-0.331) Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 12 weeks: Placebo vs Risperidone 2 mg/d-SMD = -0.752(-1.029,-0.475) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Placebo vs Risperidone 0.5mg/d-SMD = -0.19(-0.446,0.066) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Placebo vs Risperidone 1 mg/d-SMD = -0.332(-0.599,-0.065) Dementia_global-Change in BEHAVE-AD (total) at 12 weeks: Placebo vs Risperidone 2 mg/d-SMD = -0.601(-0.875,-0.327) Dementia_psychosis-Change in BEHAVE-AD (psychosis) at 12 weeks: Placebo vs Risperidone 0.5mg/d-SMD = -0.051(-0.307, 0.204) Dementia_psychosis-Change in BEHAVE-AD (psychosis) at 12 weeks: Placebo vs Risperidone 1 mg/d-SMD = -0.154(-0.419,0.111) Dementia_psychosis-Change in BEHAVE-AD (psychosis) at 12 weeks: Placebo vs Risperidone 2 mg/d-SMD = -0.385(-0.656,-0.115) Dementia_severity-Change in CGI-S at 12 weeks: Placebo vs Risperidone 1 mg/d-WMD = -0.4(-0.596,-0.204) Dementia_severity-Change in CGI-S at 12 weeks: Placebo vs Risperidone 2 mg/d-WMD = -0.5(-0.698,-0.302)	Monitored, reported by patient
Dementia and Agitation Risperidone (Meguro K et al., 2004) Japan	NR/NR/ NR	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Dementia and Agitation Risperidone (Mertens C, 1993) Western Europe	8/0/39	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of follow-ups.	Monitored
Depression Olanzapine (Howanitz E et al., 2001) NR	2/0/14	Insufficient statistics for effect-size calculation.	Monitored
Depression Olanzapine (Kinrys G et al., 2002) US	3/0/11	Insufficient statistics for effect-size calculation.	NR
Depression Olanzapine (Rothschild AJ et al., 2004) (Corya S et al., 2002) US The HGGA Study	NR/NR/116	Depression_mood-Change in HAM-D24 at 8 weeks: Placebo vs Olanzapine-SMD = -0.282(-0.573, 0.008) Depression_mood Comparison of interest not reported. Depression_severity-Change in CGI-S at 8 weeks: Placebo vs Olanzapine-WMD = -0.2(-0.441, 0.041) Depression_severity Comparison of interest not reported.	Monitored, reported by patient
Depression Olanzapine (Shi L et al., 2004) US, Australia/NZ, Europe, Colombia	397/57/ 573	Depression_qol-Change in SF-36 at 8 weeks: Placebo vs Olanzapine-SMD = 0.234(0.061,0.407)	NR
Depression Olanzapine (Tohen M et al., 2003) US, Australia/NZ, Europe, Colombia	397/57/ 788	Depression_mood-Change in MADRS at 8 weeks: Placebo vs Olanzapine-SMD = -0.233(-0.381, -0.085) Depression_severity-Change in CGI-S at 8 weeks: Placebo vs Olanzapine-WMD = -0.3(-0.423, -0.177)	Monitored
Depression Olanzapine (Tohen M et al., 2000) US The Olanzapine HGGW Study	52/4/115	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored, reported by patient

Condition, Drug Author, Year Country, Trial named	**Withdrawn/Lost to FU/ Analyzed**	**Results**	**Method of adverse events assessment**
Depression Olanzapine (Tohen M et al., 1999) US The Olanzapine HGEH Study	NR/NR/139	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored
Depression Olanzapine (Tohen M et al., 2003) US	NR/NR/66	Insufficient statistics for effect-size calculation.	NR
Depression Olanzapine (Tollefson GD et al., 1999) US Collaborative Crossover Study	11/0/95	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored, reported by patient
Dementia-Agitation Olanzapine & Risperidone (van Reekum R et al., 2002) Canada	16/0/33	Dementia_global Not a comparison of interest for statistical analysis.	Monitored
Depression Quetiapine (Calabrese J et al., 2004) US	NR/NR/511	Depression_mood-Change in MADRS at 8 weeks: Placebo vs Quetiapine 300 mg/d-SMD = -0.829(-1.05,-0.608) Depression_mood-Change in MADRS at 8 weeks: Placebo vs Quetiapine 600 mg/d-SMD = -0.868(-1.091,-0.645)	Monitored, reported by patient
Depression Risperidone (Mintzer J et al., 2004) US	NR/NR/ 355	Dementia_psychosis-Change in BEHAVE-AD (psychosis) at 8 weeks: Placebo vs Risperidone-SMD = -0.308(-0.502, -0.114) Dementia_agitation-Change in BEHAVE-AD (aggressiveness) at 8 weeks: Placebo vs Risperidone-SMD = -0.228(-0.422, -0.035) Dementia_global-Change in BEHAVE-AD (total) at 8 weeks: Placebo vs Risperidone-SMD=-0.153(-0.346, 0.040)	Monitored
Depression Risperidone (Gharabawi GM et al., 2004) (Gharabawi GM et al., 2004) NR ARISe-RD Study	17/8/48	Insufficient statistics for effect-size calculation.	Monitored

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Depression Ziprasidone (Daniels DG et al., 1999) US & Canada The Ziprasidone Study	NR/NR/302	Depression_mood-Change in MADRS at 6 weeks: Placebo vs Ziprasidone 80 mg/d-SMD = -0.117 (-0.402,0.169) Depression_mood-Change in MADRS at 6 weeks: Placebo vs Ziprasidone 160 mg/d-SMD = -0.298(-0.585,-0.011) Depression_severity-Change in CGI-S at 6 weeks: Placebo vs Ziprasidone 80 mg/d-WMD = -0.3 (-0.534,-0.066) Depression_severity-Change in CGI-S at 6 weeks: Placebo vs Ziprasidone 160 mg/d-WMD = -0.6 (-0.835,-0.365)	Monitored, reported by patient, clinical observation
Depression Ziprasidone (Keck P Jr et al., 1998) US The Ziprasidone Study	62/1/139	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Monitored, reported by patient, clinical observation
Depression and PTSD Risperidone (Bartzokis G et al., 2004) US	17/8/1948	Depression_mood-Change in HAM-D at 16 weeks: Placebo vs Risperidone-SMD = -0.447(-1.072, 0.178) PTSD_depression-Change in CAPS-TOTAL at 6 weeks: Placebo vs Risperidone-SMD = -0.441(-1.022, 0.139)	Monitored, reported by patient, .
Depression and PTSD Risperidone (Padala PR et al., 2005) US	NR/NR/15	PTSD_depression-Change in CAPS-TOTAL at 10 weeks: Placebo vs Risperidone-SMD = -1.809(-3.054, -0.564)	Monitored
Depression and PTSD Risperidone (Reich DB et al., 2004) US	NR/NR/21	PTSD-Change in CAPS-2 TOTAL at 8 weeks: Placebo vs Risperidone-SMD = -0.519(-1.398,0.361)	Monitored
OCD Olanzapine (Bystritsky A et al., 2004) US	8/0/18	OCD-Change in Y-BOCS at 6 weeks: Placebo vs Olanzapine-WMD = -5.7(-10.7,-0.7) OCD-Change in Number of Responders at 6 weeks: Placebo vs Olanzapine-RR = 13(0.8,209.4)	Monitored

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
OCD Risperidone (Buchsbaum MS, 2003) NR	NR/NR/15	Insufficient statistics for effect-size calculation.	NR
OCD Risperidone (Erzegovesi S et al., 2005) Western Europe	1/0/39	OCD-Change in Y-BOCS at 6 weeks: Placebo vs Risperidone-WMD = 0.89 (-2.5,4.3) OCD-Change in Number of Responders at 6 weeks: Placebo vs Risperidone-RR = 2.5(0.6,9.9)	NR
OCD Risperidone (Hollander E et al., 2003) US	3/0/16	OCD-Change in Y-BOCS at 8 weeks: Placebo vs Risperidone-WMD = -4.9 (-13.9,4.096) OCD-Change in Number of Responders at 8 weeks: Placebo vs Risperidone-RR = 5.7(0.4,90.8)	Monitored, elicited by investigator
PTSD Olanzapine (Butterfield MI et al., 2001) US	4/0/11	PTSD-Change in SIP at 10 weeks: Placebo vs Olanzapine-SMD = 0.182 (-0.894,1.257)	Reported by patient
PTSD Olanzapine (Stein MB et al., 2002) US	5/2/2014	Olanzapine was associated with a greater reduction than placebo in depressive symptoms as measured by the CES-D. SMD = -.726 (-1.659, .207).	NR
PTSD Risperidone (Hamner MB et al., 2003) US	15/0/37	Rejected from meta-analysis because outcomes were measured at less than 6 weeks of followups.	Elicited by investigator
PTSD Risperidone (Monnelly EP et al., 2003) US	1/0/15	Outcome of interest for statistical analysis not reported.	NR
Personality Disorder Olanzapine (Bogenschutz MP et al., 2004) US	8/7/1935	Personality Disorder-Change in CGI-BPD at 12 weeks: Placebo vs Olanzapine-SMD = -0.667 (-1.351,0.018)	Monitored

Condition, Drug Author, Year Country, Trial named	Withdrawn/Lost to FU/ Analyzed	Results	Method of adverse events assessment
Personality Disorder Olanzapine (Zanarini MC et al., 2001) US	8/11/2028	Personality Disorder-Change in SCL90-ANXIETY at 24 weeks: Placebo vs Olanzapine-SMD = -0.32 (-1.118,0.478)	Monitored, elicited by investigator
Personality Disorder Risperidone (Koenigsberg HW et al., 2003) US	10/1/23	Personality Disorder-Change in PANSS-TOTAL at 9 weeks: Placebo vs Risperidone-SMD = -1.624(-2.595, -0.653)	NR
Tourettes Ziprasidone (Sallee FR et al., 2000) US	4/0/28	Tourettes-Change in YALE GLOBAL Tic at 8 weeks: Placebo vs Ziprasidone-SMD = -0.563(-1.346, 0.22)	Monitored, reported by patient, clinical observation
Dementia and Agitation Aripiprazole (Breder C et al., 2004) NR	NR/NR/274	Insufficient statistics for effect-size calculation.	NR
Dementia and Agitation Aripiprazole (De Deyn P et al., 2005) NR	36/0/203	Dementia_global-Change in NPI-Total at 10 weeks: Placebo vs Aripiprazole-SMD = 0.847(0.56,1.135) Dementia_psychosis-Change in NPI-Psychosis at 10 weeks: Placebo vs Aripiprazole-SMD = 0.424(0.146,0.702) Dementia_severity-Change in CGI-S at 10 weeks: Placebo vs Aripiprazole-SMD = -1.034(-1.327,-0.74)	Monitored
Dementia and Agitation Aripiprazole (Streim JE et al., 2004) US	NR/NR/249	Insufficient statistics for effect-size calculation.	NR
Depression Aripiprazole (McQuade R et al., 2004) NR	NR/NR/67	Depression_mood-Change in MADRS at 26 weeks: Placebo vs Aripiprazole-SMD = -0.298(-0.612,0.016)	Monitored
Depression Olanzapine (Kennedy J et al., 2005) US	92/3/173	Dementia_cognition-Change in ADAS-Cog at 26 weeks: Placebo vs Olanzapine-SMD = 0.145(-0.109,0.398) Dementia_psychosis-Change in NPI-Psychosis at 26 weeks: Placebo vs Olanzapine-SMD = -0.015(-0.269,0.239)	Monitored, reported by patient

Condition, Drug Author, Year Country, Trial named	**Withdrawn/Lost to FU/ Analyzed**	**Results**	**Method of adverse events assessment**
Depression and Personality Disorder Olanzapine (Soler J et al., 2005) Western Europe	NR/NR/60	Depression_mood-Change in HAM-D at 12 weeks: Placebo vs Olanzapine-SMD = -2.438(1.765,3.111) Depression_severity-Change in CGI-S at 12 weeks: Placebo vs Olanzapine-WMD = -11.87(-14.226,-9.514)	Monitored
Tourettes Risperidone (Scahill L et al., 2003) US	2/0/34	Tourettes-Change in YALE GLOBAL Tic at 8 weeks: Placebo vs Risperidone-SMD = -1.09(-1.814,-0.365)	Monitored

Condition, Drug **Author, Year** **Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
Autism Risperidone (McCracken JT et al., 2002) US RUPP Autism Study	Placebo vs Risperidone: Anxiety: 20%(10/51) vs 24%(12/49) Constipation: 12%(6/51) vs 29%(14/49) Decreased appetite: 10%(5/52) vs 6%(3/49) Diarrhea: 22%(11/51) vs 18%(9/49) Dizziness: 4%(2/51) vs 16%(8/49) Drooling: 6%(3/51) vs 27%(13/49) Drowsiness: 12%(6/51) vs 49%(24/49) Dry mouth: 10%(5/51) vs 18%(9/49) Dyskinesia: 6%(3/51) vs 12%(6/49) Earache: 8%(4/51) vs 4%(2/49) Elevated serum glutamic-pyruvic transaminase level: 2%(1/51) vs 0%(0/49) Enuresis: 29%(15/51) vs 31%(15/49) Fatigue: 27%(14/51) vs 59%(29/49) Fever in association with a documented, time-limited illness: 20%(10/51) vs 16%(8/49) Headache: 12%(6/51) vs 18%(9/49) Increased appetite (mild): 25%(13/51) vs 49%(24/49) Increased appetite (moderate): 4%(2/51) vs 24%(12/49) Increased thirst: 10%(5/51) vs 12%(6/49) Insomnia: 29%(15/51) vs 14%(7/49) Muscle rigidity: 2%(1/51) vs 10%(5/49) Nasal congestion: 39%(20/51) vs 51%(25/49) Nausea: 10%(5/51) vs 8%(4/49) Nonspecific, clinically insignificant change in cardiac conduction: 2%(1/51) vs 0%(0/49) Restlessness: 6%(3/51) vs 6%(3/49) Serum glutamic-oxaloacetic transaminase more than twice upper limit of normal range at 8 wks: 2%(1/51) vs 2%(1/49) Skin irritation: 14%(7/51) vs 22%(11/49) Sleep problems: 18%(9/51) vs 22%(11/49) Sore throat: 2%(1/51) vs 10%(5/49) Stomachache: 18%(9/51) vs 10%(5/49) Tachycardia: 2%(1/51) vs 12%(6/49) Tremor: 2%(1/51) vs 14%(7/49) Upper respiratory tract infection: 4%(2/51) vs 10%(5/49) Vomiting: 24%(12/51) vs 33%(16/49) Weight change in kg: Placebo-51 people (0.8 mean,2.2 SD) vs Risperidone-49 people (2.7 mean,2.9 SD)	Placebo vs Risperidone: Withdrawals: 35.3%(18/51) vs 6.1%(3/49) Withdrawals due to adverse events: 2.0%(1/51) vs 0.0%(0/49)

Condition, Drug **Author, Year** **Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
Autism Risperidone (Shea S et al., 2004) Canada RIS-CAN-23 Study	Placebo vs Risperidone: At least one adverse event: 79.5%(31/39) vs 100.0%(40/40) Abdominal pain: 7.7%(3/39) vs 20.0%(8/40) Abnormal gait: 2.6%(1/39) vs 0.0%(0/40) Accidental overdose: 2.6%(1/39) vs 2.5%(1/40) Aggressive reaction with impaired concentration (severe): 0.0%(0/39) vs 2.5%(1/40) Anorexia: 2.6%(1/39) vs 10.0%(4/40) Apathy: 0.0%(0/39) vs 12.5%(5/40) Ataxia: 2.6%(1/39) vs 0.0%(0/40) Constipation: 2.6%(1/39) vs 12.5%(5/40) Coughing: 10.3%(4/39) vs 15.0%(6/40) Diarrhea: 15.4%(6.006/39) vs 0.0%(0/40) Dyskinesia: 2.6%(1/39) vs 0.0%(0/40) EPS: 12.8%(5/39) vs 27.5%(11/40) Emotional liability: 15.4%(6.006/39) vs 0.0%(0/40) Extrapyramidal disorder: 0.0%(0/39) vs 5.0%(2/40) Extrapyramidal disorder due to accidental overdose (severe): 0.0%(0/39) vs 2.5%(1/40) Fatigue: 2.6%(1/39) vs 10.0%(4/40) Fever: 17.9%(7/39) vs 20.0%(8/40) Headache: 5.1%(2/39) vs 12.5%(5/40) Hyperkinesia and somnolence (severe): 0.0%(0/39) vs 2.5%(1/40) Hypertonia: 2.6%(1/39) vs 0.0%(0/40) Hypokinesia: 5.0%(2/39) vs 0.0%(0/40) Increased appetite: 10.3%(4/39) vs 22.5%(9/40) Influenza-like symptoms: 5.1%(2/39) vs 10.0%(4/40) Insomnia: 15.4%(6/39) vs 15.0%(6/40) Insomnia & sunken eyes (severe): 2.6%(1/39) vs 0.0%(0/40) Involuntary muscle contractions: 2.6%(1/39) vs 0.0%(0/40) Rhinitis: 10.3%(4/39) vs 27.5%(11/40) Saliva increased: 2.6%(1/39) vs 10.0%(4/40) Somnolence: 7.7%(3/39) vs 72.5%(29/40) Somnolence (severe): 0.0%(0/39) vs 2.5%(1/40) Tachycardia: 0.0%(0/39) vs 12.5%(5/40) Tardive dyskinesia: 2.6%(1/39) vs 0.0%(0/40) Tremor: 0.0%(0/39) vs 10%(4/40) Upper respiratory tract infection: 15.4%(6/39) vs 37.5%(15/40) Vomiting: 15.4%(6/39) vs 15.0%(6/40) Weight increase: 2.6%(1/39) vs 10.0%(4/40) Weight increase (severe): 0.0%(0/39) vs 2.5%(1/40) Weight change in kg: Placebo-39 people (1.0 mean,1.6 SD) vs Risperidone-40 people (2.7 mean,2.0 SD)	Placebo vs Risperidone: Withdrawals: 12.8%(5/39) vs 5.0%(2/40) Withdrawals due to adverse events: 2.6%(1/39) vs 2.5%(1/40)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia and Agitation Olanzapine (De Deyn PP et al., 2004) Europe, Australia/NZ, South Africa F1D-MC-HGIV Study	Data not reported by intervention group.	Placebo vs Olanzapine 1 mg/d vs Olanzapine 2.5 mg/d vs Olanzapine 5 mg/d vs Olanzapine 7.5mg/d: Withdrawals: 29.5%(38/129) vs 34.1%(44/129) vs 24.6%(33/134) vs 24.8%(31/125) vs 28.8%(38/132) Withdrawals due to adverse events: 3.9%(5/129) vs 9.3%(12/129) vs 6.7%(9/134) vs 7.2%(9/125) vs 9.8%(13/132)
Dementia and Agitation Olanzapine (Street JS et al., 2000) US HGEU Study	Placebo vs Olanzapine 5 mg/d vs Olanzapine 10 mg/d vs Olanzapine 15 mg/d: Abnormal gait: 2.1%(1/47) vs 19.6%(11/56) vs 14.0%(7/50) vs 17.0%(9/53) Accidental injury: 27.7%(13/47) vs 25.0%(14/56) vs 24.0%(12/50) vs 37.7%(20/53) Agitation: 8.5%(4/47) vs 8.9%(5/56) vs 12.0%(6/50) vs 11.3%(6/53) Anorexia: 8.5%(4/47) vs 1.8%(1/56) vs 4.0%(2/50) vs 15.1%(8/53) Cough increased: 6.4%(3/47) vs 12.5%(7/56) vs 10.0%(5/50) vs 7.5%(4/53) Ecchymosis: 14.9%(7/47) vs 8.9%(5/56) vs 12.0%(6/50) vs 15.1%(8/53) Fever: 2.1%(1/47) vs 8.9%(5/56) vs 14.0%(7/50) vs 13.2%(7/53) Nervousness: 4.3%(2/47) vs 7.1%(4/56) vs 12.0%(6/50) vs 1.9%(1/53) Pain: 10.6%(5/47) vs 14.3%(8/56) vs 12.0%(6/50) vs 24.5%(13/53) Peripheral edema: 6.4%(3/47) vs 3.6%(2/56) vs 12.0%(6/50) vs 7.5%(4/53) Somnolence: 6.4%(3/47) vs 25.0%(14/56) vs 26.0%(13/50) vs 35.8%(19/53) Weight loss: 6.4%(3/47) vs 0.0%(0/56) vs 4.0%(2/50) vs 11.3%(6/53)	Placebo vs Olanzapine 5 mg/d vs Olanzapine 10 mg/d vs Olanzapine 15 mg/d: Withdrawals: 23.4%(11/47) vs 19.6%(11/56) vs 28.0%(14/50) vs 34.0%(18/53) Withdrawals due to adverse events: 4.3%(2/47) vs 10.7%(6/56) vs 8.0%(4/50) vs 17.0%(9/53)
Dementia and Agitation Olanzapine & Risperidone (Ruths S et al., 2004) Western Europe	Data not reported by intervention group.	Placebo vs Haloperidol, Risperidone, or Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
Dementia and Agitation Quetiapine (Zhong X et al., 2004) US	Placebo vs Quetiapine 200 mg/d vs Quetiapine 100 mg/d: Death: 1.1%(0.913/83) vs 1.7%(2.125/125) vs 0.6%(0.75/125)	Placebo vs Quetiapine 200 mg/d vs Quetiapine 100 mg/d: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
Dementia and Agitation Risperidone (Ballard CG et al., 2004) UK	Placebo vs Active treatment (risperidone, thioridazine, haloperidol, trifluoperazine, chlorpromazine): Death: 7.0%(3/46) vs 6.0%(3/54)	Placebo vs Active treatment (risperidone, thioridazine, haloperidol, trifluoperazine, chlorpromazine): Withdrawals: 30.0%(14/46) vs 26.0%(14/54) Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Dementia and Agitation Risperidone (Brodaty H et al., 2003) Australia/New Zealand	Placebo vs Risperidone: Aggressive reaction: 10.6%(18/170) vs 5.4%(9/167) Agitation: 24.7%(42/170) vs 19.8%(33/167) Cerebrovascular adverse event: 1.8%(3/170) vs 9.0%(15/167) Conjunctivitis: 10.6%(18/170) vs 12.0%(20/167) Constipation: 15.3%(26/170) vs 11.4%(19/167) Coughing: 2.9%(5/170) vs 5.4%(9/167) Death: 2.4%(4/170) vs 3.6%(6/167) Diarrhea: 12.9%(22/170) vs 3.0%(5/167) Dyskinesia: 5.3%(9/170) vs 0.6%(1/167) Edema peripheral: 3.5%(6/170) vs 7.8%(13/167) Extrapyramidal disorder: 2.9%(5/170) vs 6.0%(10/167) Falls: 27.1%(46/170) vs 25.1%(42/167) Fever: 2.4%(4/170) vs 5.4%(9/167) Gait abnormal: 1.2%(2/170) vs 6.0%(10/167) Headache: 6.5%(11/170) vs 4.8%(8/167) Infection: 7.1%(12/170) vs 3.6%(6/167) Injury: 37.1%(63/170) vs 35.9%(60/167) Life-threatening, requiring hospitalization or resulting in significant disability or incapacity.: 8.8%(15/170) vs 16.8%(28/167) Purpura: 15.9%(27/170) vs 18.0%(30/167) Rash: 5.3%(9/170) vs 7.8%(13/167) Skin disorder: 9.4%(16/170) vs 10.8%(18/167) Skin ulceration: 6.5%(11/170) vs 7.2%(12/167) Somnolence: 25.3%(43/170) vs 36.5%(61/167) Stroke: 0.0%(0/170) vs 3.0%(5/167) TIA: 0.0%(0/170) vs 0.6%(1/167) Total patients with adverse events: 92.4%(157/170) vs 94.0%(157/167) Tremor: 1.8%(3/170) vs 6.0%(10/167) Upper respiratory tract infection: 8.8%(15/170) vs 7.8%(13/167) Urinary tract infection: 14.7%(25/170) vs 23.4%(39/167) Vomiting: 7.6%(13/170) vs 8.4%(14/167)	Placebo vs Risperidone: Withdrawals: 32.9%(56/170) vs 26.9%(45/167) Withdrawals due to adverse events: 8.2%(13.94/170) vs 13.2% (22.044/167)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia and Agitation Risperidone (Katz IR et al., 1999) US The Risperidone Study	Placebo vs Risperidone 0.5mg/d vs Risperidone 1 mg/d vs Risperidone 2 mg/d: Experienced 1 or more serious adverse events during the trial or in the subsequent 30 days.: 12.9%(21/163) vs 10.7%(16/149) vs 16.2%(24/148) vs 17.6%(29/165) At least one adverse event: 84.7%(138/163) vs 83.9%(125/149) vs 81.8%(121/148) vs 88.5%(146/165) Agitation: 10.4%(17/163) vs 7.4%(11/149) vs 5.4%(8/148) vs 8.5%(14/165) Coughing: 8.0%(13/163) vs 10.7%(16/149) vs 5.4%(8/148) vs 8.5%(14/165) Death: 3.1%(5/163) vs 4.0%(6/149) vs 8.8%(13/148) vs 3.6%(6/165) Extrapyramidal disorder: 7.4%(12/163) vs 6.7%(10/149) vs 12.8%(19/148) vs 21.2%(35/165) Falls: 20.2%(33/163) vs 16.1%(24/149) vs 12.8%(19/148) vs 24.8%(41/165) Fever: 7.4%(12/163) vs 10.1%(15/149) vs 7.4%(11/148) vs 14.5%(24/165) Injury: 37.4%(61/163) vs 32.9%(49/149) vs 28.4%(42/148) vs 31.5%(52/165) Pain: 8.0%(13/163) vs 8.1%(12/149) vs 2.7%(4/148) vs 10.3%(17/165) Peripheral edema: 5.5%(9/163) vs 16.1%(24/149) vs 12.8%(19/148) vs 18.2%(30/165) Purpura: 11.7%(19/163) vs 16.8%(25/149) vs 12.2%(18/148) vs 10.3%(17/165) Rhinitis: 5.5%(9/163) vs 4.7%(7/149) vs 6.1%(9/148) vs 10.3%(17/165) Somnolence: 8.0%(13/163) vs 10.1%(15/149) vs 16.9%(25/148) vs 27.9%(46/165) Tardive dyskinesia: 0.6%(1/163) vs 0.0%(0/149) vs 0.0%(0/148) vs 0.0%(0/165) Upper respiratory tract infection: 3.7%(6/163) vs 10.1%(15/149) vs 7.4%(11/148) vs 5.5%(9/165) Urinary tract infection: 12.9%(21/163) vs 16.1%(24/149) vs 12.8%(19/148) vs 21.2%(35/165)	Placebo vs Risperidone 0.5mg/d vs Risperidone 1 mg/d vs Risperidone 2 mg/d: Withdrawals: 27.0%(44/163) vs 21.5%(32/149) vs 30.4%(45/148) vs 41.8%(69/165) Withdrawals due to adverse events: 12.3%(20/163) vs 8.1%(12/149) vs 16.2%(24/148) vs 24.2%(40/165)
Dementia and Agitation Risperidone (Meguro K et al., 2004) Japan	No adverse events reported.	Non-risperidone (no treatment) vs Risperidone: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
Dementia and Agitation Risperidone (Mertens C, 1993) Western Europe	Placebo vs Risperidone: At least one adverse event: 42.1%(8/19) vs 55.0%(11/20) At least one serious adverse event: 0.0%(0/19) vs 5.0%(1/20) Abnormal ECG values: 31.6%(6/19) vs 35.0%(7/20) Death: 0.0%(0/19) vs 5.0%(1/20) No. of pts with code 4: .%(16/19) vs .%(9/20)	Placebo vs Risperidone: Withdrawals: 21.1%(4/19) vs 20.0%(4/20) Withdrawals due to adverse events: 0.0%(0/19) vs 10.0%(2/20)
Depression Olanzapine (Howanitz E et al., 2001) NR	Olanzapine vs Placebo: Occurance of one adverse event: 0.0%(0/8) vs 12.5%(1/8)	Olanzapine vs Placebo: Withdrawals: 12.5%(1/8) vs 12.5%(1/8) Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine (Kinrys G et al., 2002) US	Adverse events not reported.	Placebo vs Olanzapine: Withdrawals: 0.0%(0/5) vs 33.3%(3/9) Withdrawals due to adverse events: 0.0%(0/5) vs 0.0%(0/9)
Depression Olanzapine (Rothschild AJ et al., 2004) (Corya S et al., 2002) US The HGGA Study	Placebo vs Olanzapine vs Olanzapine + fluoxetine: At least one adverse event: 83.3%(83.3/100) vs 79.2%(79.992/101) vs 81.0%(38.88/48) Ambylopia (blurred vision): 5.0%(5/100) vs 1.0%(1.01/101) vs 10.4%(4.992/48) Dry mouth: 8.0%(8/100) vs 24.8%(25.048/101) vs 10.4%(4.992/48) GGT increase: 0.0%(0/100) vs 0.0%(0/101) vs 4.2%(2.016/48) Insomnia: 20.0%(20/100) vs 7.9%(7.979/101) vs 10.4%(4.992/48) Peripheral edema: 0.0%(0/100) vs 6.9%(6.969/101) vs 10.4%(4.992/48) Somnolence: 5.0%(5/100) vs 18.8%(18.988/101) vs 25.0%(12/48) Vomiting: 10.0%(10/100) vs 3.0%(3.03/101) vs 2.1%(1.008/48) Weight gain: 2.0%(2/100) vs 10.9%(11.009/101) vs 4.2%(2.016/48)	Placebo vs Olanzapine vs Olanzapine + fluoxetine: Withdrawals: 59.0%(59/100) vs 55.4%(56/101) vs 50.0%(24/48) Withdrawals due to adverse events: 6.0%(6/100) vs 8.9%(9/101) vs 18.8%(9/48)
Depression Olanzapine (Shi L et al., 2004) US, Australia/NZ, Europe, Colombia	No adverse events reported.	Placebo vs Olanzapine vs Olanzapine + Fluoxetine: Withdrawals: 51.6%(191/370) vs 61.5%(232/377) vs 36.0%(31/86) Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Olanzapine (Tohen M et al., 2003) US, Australia/NZ, Europe, Colombia	Placebo vs Olanzapine vs Olanzapine + fluoxetine: 7% or greater weight gain: 0.3%(1.131/377) vs 18.7%(69.19/370) vs 19.5%(16.77/86) Asthenia: 3.2%(12.064/377) vs 9.7%(35.89/370) vs 12.8%(11.008/86) Diarrhea: 6.6%(24.882/377) vs 6.5%(24.05/370) vs 18.6%(15.996/86) Dry mouth: 6.1%(22.997/377) vs 11.1%(41.07/370) vs 16.3%(14.018/86) Headache: 18.6%(70.122/377) vs 12.4%(45.88/370) vs 14.0%(12.04/86) Increase in high supine systolic blood pressure: 1.7%(6.409/377) vs 0.6%(2.22/370) vs 4.9%(4.214/86) Increased appetite: 5.0%(18.85/377) vs 13.5%(49.95/370) vs 12.8%(11.008/86) Insomnia: 15.1%(56.927/377) vs 8.4%(31.08/370) vs 9.3%(7.998/86) Nausea: 8.8%(33.176/377) vs 4.3%(15.91/370) vs 11.6%(9.976/86) Nervousness: 8.0%(30.16/377) vs 10.5%(38.85/370) vs 9.3%(7.998/86) Orthostatic hypotension: 1.4%(5.278/377) vs 1.4%(5.18/370) vs 7.3%(6.278/86) Somnolence: 12.5%(47.125/377) vs 28.1%(103.97/370) vs 20.9%(17.974/86) Treatment-emergent QTc intervals of 470 milliseconds or greater: 0.3%(1/377) vs 0.3%(1/370) vs 0.0%(0/86) Treatment-emergent glucose elevation of 200 mg/dL or greater: 0.3%(1.131/377) vs 1.4%(5.18/370) vs 1.5%(1.29/86) Weight gain: 2.7%(10.179/377) vs 17.3%(64.01/370) vs 17.4%(14.964/86) Weight change in kg: Placebo-377 people (-0.47 mean,2.62 SD) vs Olanzapine-370 people (2.59 mean,3.24 SD) vs Olanzapine + Fluoxetine-86 people (2.79 mean,3.23 SD)	Placebo vs Olanzapine vs Olanzapine + fluoxetine: Withdrawals: 5.0%(19/377) vs 9.2%(34/370) vs 2.3%(2/86) Withdrawals due to adverse events: 61.5%(232/377) vs 51.6%(191/370) vs 36.0%(31/86)
Depression Olanzapine (Tohen M et al., 2000) US The Olanzapine HGGW Study	Placebo vs Olanzapine: Agitation: 25.0%(15/60) vs 9.1%(5/55) Anxiety: 15.0%(9/60) vs 3.6%(2/55) Asthenia: 5.0%(3/60) vs 10.9%(6/55) Constipation: 8.3%(5/60) vs 10.9%(6/55) Dizziness: 6.7%(4/60) vs 12.7%(7/55) Dry mouth: 5.0%(3/60) vs 16.4%(9/55) Dyspepsia: 5.0%(3/60) vs 12.7%(7/55) Headache: 21.7%(13/60) vs 18.2%(10/55) Hostility: 10.0%(6/60) vs 1.8%(1/55) Nervousness: 20.0%(12/60) vs 9.1%(5/55) Personality disorder: 11.7%(7/60) vs 1.8%(1/55) Somnolence: 8.3%(5/60) vs 38.2%(21/55) Weight change in kg: Placebo-60 people (0.45 mean,2.31 SD) vs Olanzapine-55 people (2.11 mean,2.83 SD)	Placebo vs Olanzapine: Withdrawals: 58.3%(35/60) vs 38.2%(21/55) Withdrawals due to adverse events: 1.7%(1/60) vs 3.6%(2/55)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Olanzapine (Tohen M et al., 1999) US The Olanzapine HGEH Study	Placebo vs Olanzapine: Agitation: 23.2%(16/69) vs 18.6%(13/70) Anxiety: 10.1%(7/69) vs 14.3%(10/70) Asthenia: 7.2%(5/69) vs 18.6%(13/70) Constipation: 2.9%(2/69) vs 11.4%(8/70) Depression: 11.6%(8/69) vs 12.9%(9/70) Dizziness: 5.8%(4/69) vs 22.9%(16/70) Dry mouth: 8.7%(6/69) vs 25.7%(18/70) Headache: 15.9%(11/69) vs 17.1%(12/70) Hostility: 11.6%(8/69) vs 8.6%(6/70) Increased ALT/SGPT values: 0.0%(0/69) vs 17.6%(12.32/70) Nervousness: 13.0%(9/69) vs 8.6%(6/70) Pain: 4.3%(3/69) vs 11.4%(8/70) Personality disorder: 11.6%(8/69) vs 7.1%(5/70) Somnolence: 17.4%(12/69) vs 32.9%(23/70) Weight gain: 1.4%(1/69) vs 11.4%(8/70) Weight change in kg: Placebo-69 people (-0.44 mean, 2.35 SD) vs Olanzapine-70 people (1.65 mean,2.54 SD)	Placebo vs Olanzapine: Withdrawals: 65.2%(45/69) vs 38.6%(27/70) Withdrawals due to adverse events: 2.9%(2/69) vs 0.0%(0/70)
Depression Olanzapine (Tohen M et al., 2003) US	No adverse events reported.	Placebo vs Olanzapine: Withdrawals: 90.4%(122.944/136) vs 76.4% (171.9/225) Withdrawals due to adverse events: Not reported
Depression Olanzapine (Tollefson GD et al., 1999) US Collaborative Crossover Study	Placebo vs Olanzapine: Delusions: 22.6%(10.17/45) vs 7.5%(3.75/50)	Placebo vs Olanzapine: Withdrawals: 26.7%(12/45) vs 32.0%(16/50) Withdrawals due to adverse events: 6.7%(3/45) vs 14.0%(7/50)
Dementia-Agitation Olanzapine & Risperidone (van Reekum R et al., 2002) Canada	Data not reported by interventions.	Placebo vs Anti-psychotics (risperidone, thioridazine, loxapine, perphenazine, olanzapine, haloperidol, nozinan): Withdrawals: 58.8%(10/17) vs 41.2%(7/17) Withdrawals due to adverse events: 58.8%(10/17) vs 41.2%(7/17)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Quetiapine (Calabrese J et al., 2004) US	Placebo vs Quetiapine 300 mg/d vs Quetiapine 600 mg/d: Constipation: 4.4%(8/181) vs 11.7%(21/181) vs 11.1%(20/180) Dizziness: 8.3%(15/181) vs 16.8%(30/181) vs 22.8%(41/180) Dry mouth: 7.8%(14/181) vs 44.1%(79/181) vs 40.6%(73/180) Mania: 4.0%(7.24/181) vs 3.0%(5.43/181) vs 2.0%(3.6/180) Sedation: 6.1%(11/181) vs 29.6%(53/181) vs 32.2%(58/180) Somnolence: 8.3%(15/181) vs 27.4%(49/181) vs 24.2%(44/180) Weight change in kg: Placebo-181 people (0.1 mean, SD NR) vs Quetiapine 300 mg/d-181 people (0.4 mean, SD NR) vs Quetiapine 600 mg/d-180 people (1.6 mean, SD NR)	Placebo vs Quetiapine 300 mg/d vs Quetiapine 600 mg/d: Withdrawals: 6.6%(12/181) vs 5.0%(9/181) vs 5.6%(10/180) Withdrawals due to adverse events: Not reported
Depression Risperidone (Mintzer J et al., 2004) US	Placebo vs Risperidone: Agitation: 6.7%(16/238) vs 8.1%(19/235) Cerebrovascular disorder: 0.4%(1/238) vs 1.7%(4/235) Death: 2.5%(6/238) vs 3.8%(9/235) EPS-related AEs: 3.4%(8/238) vs 8.5%(20/235) Edema-related AEs: 4.6%(11/238) vs 5.1%(12/235) Fall: 12.6%(30/238) vs 11.1%(26/235) Glucose-related AEs: 2.1%(5/238) vs 1.7%(4/235) Hematoma: 5.0%(12/238) vs 3.4%(8/235) Injury: 10.5%(25/238) vs 9.4%(22/235) Insomnia: 5.9%(14/238) vs 5.5%(13/235) Prolactin-related AEs: 0.0%(0/238) vs 0.0%(0/235) Somnolence: 4.6%(11/238) vs 16.2%(38/235) Stroke: 0.4%(1/238) vs 0.4%(1/235) Urinary tract infection: 10.1%(24/238) vs 9.4%(22/235)	Placebo vs Risperidone: Withdrawals: 24.8%(59/238) vs 25.1%(59/235) Withdrawals due to adverse events: 10.1% (24.038/238) vs 10.6% (24.91/235)
Depression Risperidone (Gharabawi GM et al., 2004) (Gharabawi GM et al., 2004) NR ARISe-RD Study	Placebo vs Risperidone + citalopram: Dizziness: 2.5%(3/119) vs 5.7%(7/122) Fatigue: 7.6%(9/119) vs 4.9%(6/122) Headache: 5.9%(7/119) vs 11.5%(14/122) Insomnia: 5.9%(7/119) vs 3.3%(4/122) Weight Increase: 4.2%(5/119) vs 7.4%(9/122) Weight change in kg: Placebo-119 people (-0.6 kg mean, SD NR) vs Risperidone-122 people (1.2 kg mean, SD NR)	Placebo vs Risperidone + citalopram: Withdrawals: 9.3% (11.067/119) vs 11.5% (14.03/122) Withdrawals due to adverse events: 2.5%(2.975/119) vs 4.1%(5.002/122)

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression Ziprasidone (Daniels DG et al., 1999) US & Canada The Ziprasidone Study	Placebo vs Ziprasidone 80 mg/d vs Ziprasidone 160 mg/d: At least one adverse event: 86.0%(79/92) vs 87.0%(92/106) vs 89.0%(93/104) Abdominal pain: 5.0%(5/92) vs 3.0%(3/106) vs 10.0%(10/104) Agitation: 11.0%(10/92) vs 10.0%(10/106) vs 9.0%(9/104) Akathisia: 7.0%(6/92) vs 14.0%(15/106) vs 13.0%(13/104) Constipation: 14.0%(13/92) vs 7.0%(7/106) vs 14.0%(14/104) Dizziness: 9.0%(8/92) vs 9.0%(10/106) vs 17.0%(18/104) Dry mouth: 4.0%(4/92) vs 4.0%(4/106) vs 13.0%(13/104) Dyspepsia: 9.0%(8/92) vs 9.0%(10/106) vs 14.0%(14/104) Dystonia: 2.2%(2.024/92) vs 0.0%(0/106) vs 3.8%(3.952/104) Extrapyramidal syndrome: 1.0%(0.92/92) vs 2.0%(2.12/106) vs 7.0%(7.28/104) Headache: 33.0%(30/92) vs 17.0%(18/106) vs 31.0%(32/104) Impotence: 0.0%(0/92) vs 0.0%(0/106) vs 1.0%(1/104) Increased appetite: 0.0%(0/92) vs 1.9%(2/106) vs 0.0%(0/104) Insomnia: 14.0%(13/92) vs 12.0%(13/106) vs 12.0%(12/104) Male sexual dysfunction: 0.0%(0/92) vs 0.0%(0/106) vs 1.0%(1/104) Nausea: 9.0%(8/92) vs 14.0%(15/106) vs 7.0%(7/104) Pain: 9.0%(8/92) vs 6.0%(6/106) vs 10.0%(10/104) Seizure: 0.0%(0/92) vs 0.0%(0/106) vs 0.0%(0/104) Severe EPS: 0.0%(0/92) vs 0.0%(0/106) vs 1.0%(1/104) Severe adverse evens: 11.0%(10/92) vs 8.0%(8/106) vs 8.0%(8/104) Somnolence: 5.0%(5/92) vs 19.0%(20/106) vs 19.0%(20/104) Tachycardia & orthostatic hypotension: 0.0%(0/92) vs 2.0%(2.12/106) vs 1.0%(1.04/104) Vomiting: 15.0%(14/92) vs 11.0%(12/106) vs 6.0%(6/104) Weight change in kg: Placebo-92 people (0.0 mean, SD NR) vs Ziprasidone 80 mg/day-106 people (1.0 mean, SD NR) vs Ziprasidone 160 mg/day-104 people (0.0 mean, SD NR)	Placebo vs Ziprasidone 80 mg/d vs Ziprasidone 160 mg/d: Withdrawals: 50.0%(46/92) vs 48.0% (50.88/106) vs 28.0% (29.12/104) Withdrawals due to adverse events: 1.1%(1/92) vs 1.8%(2/106) vs 7.7%(8/104)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Ziprasidone (Keck P Jr et al., 1998) US The Ziprasidone Study	Placebo vs Ziprasidone 40 mg/d vs Ziprasidone 120 mg/d: At least one adverse event: 75.0%(36/48) vs 75.0%(33/44) vs 81.0%(36/47) Abdominal pain: 8.3%(4/48) vs 11.4%(5/44) vs 2.1%(1/47) Abnormal laboratory test (elevated hepatic transaminase): 0.0%(0/48) vs 0.0%(0/44) vs 2.1%(1/47) Agitation: 12.5%(6/48) vs 0.0%(0/44) vs 6.4%(3/47) Akathisia: 6.3%(3/48) vs 6.8%(3/44) vs 2.1%(1/47) Asthenia: 0.0%(0/48) vs 2.3%(1/44) vs 4.3%(2/47) Asthma: 2.1%(1/48) vs 4.5%(2/44) vs 2.1%(1/47) Back pain: 0.0%(0/48) vs 4.5%(2/44) vs 4.3%(2/47) Cogwheel rigidity: 0.0%(0/48) vs 0.0%(0/44) vs 4.3%(2/47) Constipation: 4.2%(2/48) vs 6.8%(3/44) vs 10.6%(5/47) Diarrhea: 0.0%(0/48) vs 0.0%(0/44) vs 4.3%(2/47) Dizziness: 2.1%(1/48) vs 4.5%(2/44) vs 2.1%(1/47) Dyspepsia: 6.3%(3/48) vs 11.4%(5/44) vs 6.4%(3/47) EPS: 2.1%(1/48) vs 2.3%(1/44) vs 6.4%(3/47) Headache: 20.8%(10/48) vs 18.2%(8/44) vs 21.3%(10/47) Hypertonia: 2.1%(1/48) vs 2.3%(1/44) vs 4.3%(2/47) Insomnia: 4.2%(2/48) vs 2.3%(1/44) vs 0.0%(0/47) Nausea: 4.2%(2/48) vs 6.8%(3/44) vs 6.4%(3/47) Pain: 8.3%(4/48) vs 9.1%(4/44) vs 4.3%(2/47) Peripheral edema: 0.0%(0/48) vs 0.0%(0/44) vs 4.3%(2/47) Pharyngitis: 2.1%(1/48) vs 4.5%(2/44) vs 4.3%(2/47) Rash: 0.0%(0/48) vs 6.8%(3/44) vs 2.1%(1/47) Respiratory disorder: 2.1%(1/48) vs 6.8%(3/44) vs 4.3%(2/47) Serious adverse events: 0.0%(0/48) vs 11.4%(5/44) vs 6.4%(3/47) Skin hypertrophy: 0.0%(0/48) vs 4.5%(2/44) vs 2.1%(1/47) Somnolence: 8.3%(4/48) vs 6.8%(3/44) vs 8.5%(4/47) Tremor: 0.0%(0/48) vs 0.0%(0/44) vs 6.4%(3/47) Vomiting: 4.2%(2/48) vs 4.5%(2/44) vs 2.1%(1/47)	Placebo vs Ziprasidone 40 mg/d vs Ziprasidone 120 mg/d: Withdrawals: 50.0%(24/48) vs 36.0%(16/44) vs 49.0%(23/47) Withdrawals due to adverse events: 0.0%(0/48) vs 2.0%(1/44) vs 9.0%(4/47)
Depression and PTSD Risperidone (Bartzokis G et al., 2004) US	No adverse events reported.	Placebo vs Risperidone: Withdrawals: 18.8%(6/32) vs 33.3%(11/33) Withdrawals due to adverse events: 6.3%(2/32) vs 9.1%(3/33)
Depression and PTSD Risperidone (Padala PR et al., 2005) US	No adverse events reported.	Placebo vs Risperidone: Withdrawals: Not reported Withdrawals due to adverse events: Not reported

Condition, Drug Author, Year Country, Trial named	**Adverse events reported**	**Total withdrawals Withdrawals due to adverse events**
Depression and PTSD Risperidone (Reich DB et al., 2004) US	Placebo vs Risperidone: At least one adverse event: 11.1%(1/9) vs 33.3%(4/12) Weight change in kg: Placebo-9people (1.4 kg mean, SD) vs Risperidone-12 people (1.1 kg mean, SD)	Placebo vs Risperidone: Withdrawals: 22.2%(2/9) vs 25.0%(3/12) Withdrawals due to adverse events: 0.0%(0/9) vs 8.3%(1/12)
OCD Olanzapine (Bystritsky A et al., 2004) US	No adverse events reported.	Placebo vs Olanzapine: Withdrawals: 46.2%(6/13) vs 15.4%(2/13) Withdrawals due to adverse events: 0.0%(0/13) vs 15.4%(2/13)
OCD Risperidone (Buchsbaum MS, 2003) NR	Sample size not reported by group	Placebo vs Risperidone: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
OCD Risperidone (Erzegovesi S et al., 2005) Western Europe	Placebo vs Risperidone: Mild increasing of appetite: 0.0%(0/19) vs 15.0%(3/20) Transient sedation: 0.0%(0/19) vs 35.0%(7/20)	Placebo vs Risperidone: Withdrawals: Not reported Withdrawals due to adverse events: not broken down by group
OCD Risperidone (Hollander E et al., 2003) US	Placebo vs Risperidone: At least one adverse event: 33.3%(2/6) vs 40.0%(4/10) Dizziness: 0.0%(0/6) vs 10.0%(1/10) Dry mouth: 16.7%(1/6) vs 20.0%(2/10) Sedation: 0.0%(0/6) vs 30.0%(3/10) Sexual dysfunction: 16.7%(1/6) vs 0.0%(0/10)	Placebo vs Risperidone: Withdrawals: 33.3%(2/6) vs 10.0%(1/10) Withdrawals due to adverse events: 0.0%(0/6) vs 0.0%(0/10)
PTSD Olanzapine (Butterfield MI et al., 2001) US	No adverse events reported. Weight change in lbs: Placebo-5 people (0.9 mean,0.06 SD) vs Olanzapine-10 people (11.5 mean,4.43 SD)	Placebo vs Olanzapine: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
PTSD Olanzapine (Stein MB et al., 2002) US	Placebo vs Olanzepine: Somnolence: 0.0%(0/9) vs 20.0%(2/10) Weight change in lbs: Placebo-9 people (Mean NR , SD NR) vs Olanzapine-10 people (13 mean, SD)	Placebo vs Olanzepine: Withdrawals: 22.2%(2/9) vs 30.0%(3/10) Withdrawals due to adverse events: 0.0%(0/9) vs 20.0%(2/10)
PTSD Risperidone (Hamner MB et al., 2003) US	Placebo vs Risperidone: Mild akathisia: 0.0%(0/18) vs 5.3%(1/19) Mild nausea and diarrhea: 0.0%(0/18) vs 5.3%(1/19)	Placebo vs Risperidone: Withdrawals: 33.3%(6/18) vs 47.4%(9/19) Withdrawals due to adverse events: 0.0%(0/18) vs 0.0%(0/19)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
PTSD Risperidone (Monnelly EP et al., 2003) US	Placebo vs Risperidone: Mild adverse events: 25.0%(2/8) vs 50.0%(4/8) Moderate adverse events: 12.5%(1/8) vs 0.0%(0/8) Urinary retention: 0.0%(0/8) vs 12.5%(1/8)	Placebo vs Risperidone: Withdrawals: 0.0%(0/8) vs 12.5%(1/8) Withdrawals due to adverse events: 0.0%(0/8) vs 12.5%(1/8)
Personality Disorder Olanzapine (Bogenschutz MP et al., 2004) US	Olanzapine vs Placebo: Sedation: 10.0%(2/20) vs 0.0%(0/20) Weight gain: 10.0%(2/20) vs 0.0%(0/20) Weight change in kg: Placebo-20 people (0.08 mean,4.8 SD) vs Olanzapine-20 people (3.71 mean,3.4 SD)	Olanzapine vs Placebo: Withdrawals: 50.0%(10/20) vs 35.0%(7/20) Withdrawals due to adverse events: 20.0%(4/20) vs 0.0%(0/20)
Personality Disorder Olanzapine (Zanarini MC et al., 2001) US	Placebo vs Olanzapine: Constipation: 0.0%(0/9) vs 31.6%(6/19) Mild rigidity: 0.0%(0/9) vs 5.3%(1/19) Perceived weight gain: 0.0%(0/9) vs 47.4%(9/19) Sedation: 33.3%(3/9) vs 42.1%(8/19) Self mutilative acts: 0.0%(0/9) vs 0.0%(0/19) Serious movement disorders: 0.0%(0/9) vs 0.0%(0/19) Suicidal acts: 0.0%(0/9) vs 0.0%(0/19) Tardive dyskinesia: 0.0%(0/9) vs 0.0%(0/19) Weight change in kg: Placebo-9 people (-0.78 mean,2.59 SD) vs Olanzapine-19 people (1.29 mean,2.56 SD)	Placebo vs Olanzapine: Withdrawals: 88.9%(8/9) vs 57.9%(11/19) Withdrawals due to adverse events: 0.0%(0/9) vs 31.6%(6/19)
Personality Disorder Risperidone (Koenigsberg HW et al., 2003) US	Placebo vs Risperidone: At least one adverse event: 50.0%(5/10) vs 46.7%(7/15)	Placebo vs Risperidone: Withdrawals: 30.0%(3/10) vs 46.7%(7/15) Withdrawals due to adverse events: 10.0%(1/10) vs 33.3%(5/15)
Tourettes Ziprasidone (Sallee FR et al., 2000) US	Placebo vs Ziprasidone: At least one adverse event: 58.3%(7/12) vs 100.0%(16/16) Akathisia: 0.0%(0/12) vs 6.3%(1/16) Increase in sedation score above baseline values on at least one visit: 45.0%(5/12) vs 69.0%(11/16) Increases in serum prolacin concentrations greater than 1.1 times the upper limit of normal: 0.0%(0/12) vs 31.3%(5/16) Mild gynecomastia: 0.0%(0/12) vs 6.3%(1/16) Somnolence: 0.0%(0/12) vs 6.3%(1/16) Weight change in kg: Placebo-12 people (0.8 mean,2.3 SD) vs Ziprasidone-16 people (0.7 mean,1.5 SD)	Placebo vs Ziprasidone: Withdrawals: 25.0%(3/12) vs 6.3%(1/16) Withdrawals due to adverse events: 0.0%(0/12) vs 6.3%(1/16)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Dementia and Agitation Aripiprazole (Breder C et al., 2004) NR	Placebo vs Aripiprazole vs Aripiprazole vs Aripiprazole: Accidental injury: 18.0%(22/121) vs 30.0%(35/118) vs 24.0%(29/122) vs 23.0%(29/126) Agitation: 16.0%(19/121) vs 12.0%(14/118) vs 7.0%(9/122) vs 11.0%(14/126) Anorexia: 11.0%(13/121) vs 8.0%(9/118) vs 5.0%(6/122) vs 6.0%(8/126) Asthenia: 4.0%(5/121) vs 6.0%(7/118) vs 9.0%(11/122) vs 6.0%(8/126) Death: 3.0%(4/121) vs (NR/118) vs (NR/122) vs (NR/126) EPS-related AEs: 6.0%(7/121) vs 8.0%(9/118) vs 7.0%(9/122) vs 7.0%(9/126) Ecchymosis: 10.0%(12/121) vs 9.0%(11/118) vs 5.0%(6/122) vs 8.0%(10/126) Edema peripheral: 8.0%(10/121) vs 10.0%(12/118) vs 6.0%(7/122) vs 10.0%(13/126) Extremity pain: 6.0%(7/121) vs 7.0%(8/118) vs 9.0%(11/122) vs 10.0%(13/126) Skin ulcer: 7.0%(9/121) vs 10.0%(12/118) vs 12.0%(15/122) vs 11.0%(14/126) Somnolence: 3.0%(4/121) vs 3.0%(4/118) vs 10.0%(12/122) vs 9.0%(11/126) Urinary incontinence: 2.0%(2/121) vs 2.0%(2/118) vs 10.0%(12/122) vs 6.0%(8/126) Urinary tract infection: 14.0%(17/121) vs 15.0%(18/118) vs 17.0%(21/122) vs 22.0%(28/126) Vomiting: 7.0%(9/121) vs 11.0%(13/118) vs 8.0%(10/122) vs 7.0%(9/126)	Placebo vs Aripiprazole vs Aripiprazole vs Aripiprazole: Withdrawals: (NR/121) vs (NR/118) vs (NR/122) vs (NR/126) Withdrawals due to adverse events: 3.0%(16/121) vs 8.0%(9/118) vs 18.0%(22/122) vs 25.0%(31/126)
Dementia and Agitation Aripiprazole (De Deyn P et al., 2005) NR	Placebo vs Aripiprazole: Bronchitis: 3.0%(3.1/102) vs 6.0%(6.4/106) Death: 0.0%(0/102) vs 3.8%(4/106) EPS-related AEs: 3.9%(4/102) vs 4.7%(5/106) Fractures: 2.0%(2/102) vs 4.7%(5/106) Hypertension: 5.0%(5/102) vs 4.0%(4/106) Increased QTc Interval: 1.0%(1/102) vs 1.9%(2/106) Increased lactate dehydrogenase: 1.0%(1/102) vs 0.0%(0/106) Mild transient cerebral ischemia: 1.0%(1/102) vs 0.9%(1/106) Somnolence: 1.0%(1/102) vs 8.0%(9/106) Urinary tract infection: 12.0%(12/102) vs 8.0%(9/106) Weight gain: 3.0%(3/102) vs 5.0%(5/106)	Placebo vs Aripiprazole: Withdrawals: 17.6%(18/102) vs 17.0%(18/106) Withdrawals due to adverse events: 6.9%(7/102) vs 9.4%(10/106)
Dementia and Agitation Aripiprazole (Streim JE et al., 2004) US	Placebo vs Aripiprazole: Accidental injury: 30.0%(38/125) vs 21.0%(28/131) Asthenia: 7.0%(9/125) vs 12.0%(16/131) Death: 2.4%(3/125) vs 2.3%(3/131) ECG abnormalities: (NR/125) vs (NR/131) EPS-related AEs: 4.0%(5/125) vs 5.0%(7/131) Ecchymosis: 13.0%(16/125) vs 12.0%(16/131) Hypotension and syncope: 5.0%(6/125) vs 3.0%(4/131) Rash: 12.0%(15/125) vs 10.0%(13/131) Somnolence: 4.0%(5/125) vs 14.0%(18/131) Urinary tract infection: 11.0%(14/125) vs 14.0%(18/131) Vomiting: 8.0%(10/125) vs 10.0%(13/131)	Placebo vs Aripiprazole: Withdrawals: (NR/125) vs (NR/131) Withdrawals due to adverse events: 9.0%(11/125) vs 12.0%(16/131)

Condition, Drug Author, Year Country, Trial named	Adverse events reported	Total withdrawals Withdrawals due to adverse events
Depression Aripiprazole (McQuade R et al., 2004) NR	Placebo vs Aripiprazole: Agitation: 11.0%(9/83) vs 7.0%(6/78) Akathisia: 1.2%(1/83) vs 6.5%(5/78) Anxiety: 16.0%(13/83) vs 18.0%(14/78) Depression: 14.0%(12/83) vs 11.0%(9/78) EPS: 1.2%(1/83) vs 0.0%(0/78) Headache: 17.0%(14/83) vs 8.0%(6/78) Insomnia: 20.0%(17/83) vs 16.0%(12/78) Nervousness: 5.0%(4/83) vs 10.0%(8/78) Reaction Manic: 13.0%(11/83) vs 6.0%(5/78) Somnolence: 7.2%(6/83) vs 5.2%(4/78)	Placebo vs Aripiprazole: Withdrawals: (NR/83) vs (NR/78) Withdrawals due to adverse events: 1.0%(1/83) vs 6.0%(5/78)
Depression Olanzapine (Kennedy J et al., 2005) US	Placebo vs Olanzapine: Abnormal gait: 3.3%(3/90) vs 6.7%(12/178) Accidental injury: 6.7%(6/90) vs 11.8%(21/178) Agitation: 5.7%(5/90) vs 8.4%(15/178) Amnesia: 2.2%(2/90) vs 5.6%(10/178) Anxiety: 5.7%(5/90) vs 5.6%(10/178) Asthenia: 5.7%(5/90) vs 10.1%(18/178) Cerebrovascular adverse events: 1.1%(1/90) vs 1.7%(3/178) Confusion: 2.2%(2/90) vs 6.2%(11/178) Constipation: 1.1%(1/90) vs 6.2%(11/178) Death: 1.1%(1/90) vs 0.6%(1/178) Delusions: 1.1%(1/90) vs 5.6%(10/178) Depression: 2.2%(2/90) vs 6.7%(12/178) Diarrhea: 5.7%(5/90) vs 7.3%(13/178) Dizziness: 7.8%(7/90) vs 8.4%(15/178) Extrapyramidal symptoms: (NR/90) vs (NR/178) Flu syndrome: 1.1%(1/90) vs 9.6%(17/178) Insomnia: 3.3%(3/90) vs 6.2%(11/178) Osteoporosis: 3.3%(3/90) vs 0.0%(0/178) Pain: 5.7%(5/90) vs 5.1%(9/178) Peripheral edema: 1.1%(1/90) vs 7.3%(13/178) Somnolence: 4.4%(4/90) vs 16.9%(30/178) Surgical procedure: 5.7%(5/90) vs 9.0%(16/178) Treatment-emergent central anticholinergic-like events: 10.0%(9/90) vs 22.5%(40/178) Treatment-emergent peripheral anticholinergic-like events: 3.3%(3/90) vs 11.2%(20/178) Urinary tract infection: 5.7%(5/90) vs 5.6%(10/178) Weight gain: 1.1%(1/90) vs 7.3%(13/178)	Placebo vs Olanzapine: Withdrawals: 26.7%(24/90) vs 38.2%(68/178) Withdrawals due to adverse events: 4.4%(4/90) vs 12.4%(22/178)
Depression and Personality Disorder Olanzapine (Soler J et al., 2005) Western Europe	1625 Placebo vs Olanzapine: Increased cholesterol: (NR/30) vs (NR/30) Movement disorders: (NR/30) vs (NR/30) Secondary effects: (NR/30) vs (NR/30) Weight gain: (NR/30) vs (NR/30)	Placebo vs Placebo vs Olanzapine vs Olanzapine: Withdrawals: (NR/30) vs (NR/30) vs (NR/30) vs (NR/30)

Condition, Drug **Author, Year** **Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
Tourettes Risperidone (Scahill L et al., 2003) US	Placebo vs Risperidone: Blurred vision: 0.0%(0/18) vs 12.5%(2/16) Constipation: 5.5%(1/18) vs 0.0%(0/16) Decreased appetite: 5.5%(1/18) vs 6.5%(1/16) Erectle difficulties: 0.0%(0/18) vs 13.0%(2/16) Fatigue: 5.5%(1/18) vs 37.5%(6/16) Foggy thinking: 0.0%(0/18) vs 12.5%(2/16) Headache: 17.0%(3/18) vs 0.0%(0/16) Increased appetite: 0.0%(0/18) vs 44.0%(7/16) Insomnia: 5.5%(1/18) vs 6.5%(1/16) Nausea/Vomiting: 0.0%(0/18) vs 6.5%(1/16) Sedation: 5.5%(1/18) vs 19.0%(3/16) Social phobia: 0.0%(0/18) vs 13.0%(2/16)	Placebo vs Risperidone: Withdrawals: 5.6%(1/18) vs 6.3%(1/16) Withdrawals due to adverse events: (NR/18) vs (NR/16)

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
ADL	Activities of Daily Life
AIAQ	Anger, Irritability, and Assault Questionnaire
ASI	Addiction Severity Index
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Index
BDHI	Buss-Durkee Hostility Index
BDI	Beck Depression Index
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelsen Melancholia Scale
CAPS	Clinician Administered PTSD Scale
CDSS	Calgary Depression Scale for Schizophrenia
CES-D	Center for Epidemiologic Studies Depression Scale
CGI	Clinical Global Impression Scale
CMAI	Cohen-Mansfield Agitation Inventory
CM-PNB	Cohen-Mansfield Physically Non-Aggressive Behavior
CPRS	Children's Psychiatric Rating Scale
CSDD	Cornell Scale for Depression in Dementia
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DCM	Dementia Care Mapping
DES	Dissociative Experiences Scale
DTS	Davidson Trauma Scale
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
FAST	Functional Assessment Staging Rating Scale
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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C4: Evidence Tables – Augmentation Trials

Condition, Drug Author, Year, Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/ Randomization Method Wash-out period/ Randomization Method	Allowed other medications	Method of outcome assessment Timing of assessment	Age mean/ Age range Gender Ethnicity
Depression Olanzapine (Tohen M et al., 2002) US & Canada	Design: RCT Setting: Multi-center Jadad: 3	Inclusion criteria: Previous depressed, manic, or mixed episode, YMRS ≥ 16, Treatment = lithium or valproate at therapeutic level Exclusion criteria: NR	Lithium-dosage not reported or Valproate-dosage not reported Olanzapine-10.4 mg/day average final dose, Lithium or Valproate Duration: 1.5 months	None 2-7 dy of Concomitant medication except lithium or valproate for randomization not described	Benzodiazepines	Assessed at baseline and 6 weeks: YMRS, HAM_D_HDRS, PANSS, CGI	41/NR 48% male Caucasian, NOS
Depression Quetiapine (Yargic LI et al., 2004) Turkey	Design: RCT Setting: Multi-center Jadad: 2	Inclusion criteria: HAM-D Items 10 and 11 ≥ 2, HAM-D ≥ 26 Exclusion criteria: HAM-D Item 3 > 2, Psychotic disorder, Use psychotropic medications within 4 wks, Medically significant disorders, Abnormal laboratory results, Bipolar disorder, Alcohol or substance abuse or dependency, Pregnant	Paroxetine- 27.6 mg/day average final dose Quetiapine-60 mg/day average final dose, Paroxetine- 27.0 mg/day average final dose Duration: 2.0 months	None None	NR	Assessed at baseline and 8 weeks: HAM_D_HDRS, HAM_A, CGI	35/18-65 26% male NR
OCD Quetiapine (Atmaca M et al., 2002) Turkey	Design: RCT Setting: Single center Jadad: 2	Inclusion criteria: Y-BOCS ≥ 18, CGI-I minimal improvement Exclusion criteria: NR	SRI- varied depending on drug Quetiapine-91.1 mg/day average final dose, SRI- varied depending on drug Duration: 2.0 months	3 mo of SSRIs for patients refractory to SRI monotherapy None	NR	Assessed at baseline and 8 weeks: YBOCS, CGI	28/18-49 52% male NR

Condition, Drug Author, Year, Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**
OCD Quetiapine (Denys D et al., 2004) Western Europe	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: Age 18-65, Y-BOCS ≥ 18, Y-BOCS ≥ 12, if only obsessions or compulsions were present, Refractory to SRI therapy Exclusion criteria: Tic disorder, Tourettes disorder, Major depressive disorder, Pregnant, Organic mental disorder, Seizure disorder or epilepsy or risk, Neurological disorder, Bipolar disorder	SRI- 20 to 300 mg, depending on drug Quetiapine-150 mg/day average final dose, SRI- 20 to 300 mg, depending on drug Duration: 2.0 months	None None	NR	Assessed at baseline and 8 weeks: YBOCS, HAM_D_HDRS, HAM_A, SDS, BABS, CGI	35/18-60 25% male NR
OCD Risperidone (Cavedini P et al., 2004) Western Europe	Design: RCT Setting: Single center Jadad: 4	Inclusion criteria: NR Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, Tic disorder, Medically significant disorders, Severe internal or neurological disease, Brain injury or head trauma, Alcohol or substance abuse or dependency	Fluvoxamine- 245 mg/day average final dose Fluvoxamine- 255 mg/day average final dose Risperidone-0.5 mg/day fixed single dose Duration: 3.0 months	None None	No other concomitant therapy, either pharmacologic or non-pharmacologic was allowed.	Assessed at baseline and 12 weeks: YBOCS, IGT	36/NR 37% male NR

Condition, Drug Author, Year, Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**
OCD Risperidone (McDougle CJ et al., 2000) US	Design: Trial + open label Setting: Single center Jadad: 4	Inclusion criteria: 1 year duration primary condition, CGI ≥ moderate severity, Refractory to SRI therapy Exclusion criteria: Non-healthy, Pregnant, Use psychotropic medications within 4 wks	Risperidone-2.2 mg/day average final dose, Clomipramine-250 mg/day average final dose, Fluvoxamine-300 mg/day average final dose Duration: 1.5 months	12 wk of SRI monotherapy for patients refractory to SRI monotherapy None	None	Assessed at baseline and 6 weeks: YBOCS, HAM_D_HDRS, HAM_A, Yale Global Tic, CGI	37/19-63 58% male Caucasian, African-American, Hispanic, Asian
OCD and Tourettes Olanzapine (Shapira NA et al., 2004) US	Design: RCT Setting: Single center Jadad: 3	Inclusion criteria: Age 14-70, 1 year duration primary condition, CGI ≥ moderate severity, Y-BOCS ≥ 19 Exclusion criteria: Major depressive disorder, Psychotic disorder, Bipolar disorder, Alcohol or substance abuse or dependency, Seizure disorder or epilepsy or risk, Encephalitis, Brain injury or head trauma, Medically significant disorders	Placebo-5.9 mg/day average final dose, Fluoxetine- 40 mg Olanzapine-6.1 mg/day average final dose, Fluoxetine- 40 mg Duration: 1.5 months	1 wk of Placebo for randomization not described None	NR	Assessed at baseline and 6 weeks: YBOCS	37/NR 41% male NR

Condition, Drug Author, Year, Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**
Depression Ziprasidone (Dunner D et al., 2003) US	Design: RCT Setting: NR Jadad: 1	Inclusion criteria: Age 21-65, MADRS ≥ 20, Resistant to antidepressant therapy, MADRS ≥ 30% reduction at week 7, CGI ≥ 4, Male or female Exclusion criteria: NR	Sertraline - 100-200 mg/day fixed titration schedule Ziprasidone - 80 or 160 mg/day fixed titration schedule, Sertraline - 100-200 mg/day fixed titration schedule Duration: 2.0 months	6 wk of Sertraline for non-placebo responders None	Not reported	Assessed at baseline and 8 weeks: MADRS, HAM_D_HDRS, CGI	44 / NR 48% male NR
OCD and Depression Quetiapine (Carey PD et al., 2005) Canada, South Africa ISRCTN83050762	Design: RCT Setting: Multi-center Jadad: 5	Inclusion criteria: Age 18-65, Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, CGI-I minimal improvement, CGI = worse Exclusion criteria: Lactating, Sexually active females of child bearing age not using an effective contraceptive method, Medically significant disorders, Brain injury or head trauma, Co-existing Axis -I disorder unless deemed to be secondary to OCD, Brain Surgery, Seizure disorder or epilepsy or risk, Medications that interact with Quetiapine	Placebo - 228.57 mg/day average final dose, Fluvoxamine 100-300 mg/day flexible dose, Fluoxetine 20-300 mg/day flexible dose, Paroxetine 60-300 mg/day flexible dose, Citalopram 50-300 mg/day flexible dose Quetiapine - 168.75 mg/day average final dose, Fluvoxamine 25-300 mg/day flexible dose, Fluoxetine 20-300 mg/day flexible dose, Paroxetine 50-300 mg/day flexible dose, Citalopram 60-300 mg/day flexible dose, Clomipramine 100-300 mg/day flexible dose, Sert Duration: 1.5 months	6-12 wk of SSRIs for patients refractory to SRI None	Not reported	Assessed at baseline and 6 weeks: YBOCS, CGI, MADRS, SDS, Yale Global Tic	33 / NR 46% male NR

Condition, Drug Author, Year, Country, Trial named	**Study design Setting Quality (Jadad Score)**	**Eligibility criteria**	**Interventions (drug, dose, duration)**	**Run-in period/ Randomization Method Wash-out period/ Randomization Method**	**Allowed other medications**	**Method of outcome assessment Timing of assessment**	**Age mean/ Age range Gender Ethnicity**
OCD and Depression Quetiapine (Fineberg NA et al., 2005) UK	Design: RCT Setting: NR Jadad: 3	Inclusion criteria: Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, Y-BOCS ≥ 18 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, DSM-IV Axis I disorder, not including primary condition studied or depression with MADRS < 30, Tourettes disorder, Resistant to antipsychotic treatment	Placebo - dosage not reported, Paroxetine 40-60 mg/day flexible dose, Citalopram 60-80 mg/day flexible dose, Sertraline 200 mg/day average final dose Quetiapine - 215 mg/day average final dose, Paroxetine 60 mg/day average final dose, Sertraline 75-200 mg/day flexible dose Duration: 4.0 months	None None	Not reported	Assessed at baseline and 16 weeks: YBOCS, Yale Global Tic, CGI, MADRS, NIMH-OC, Extrapyramidel side effects, SDS	38 / NR 43% male NR

Condition, Drug Author, Year, Country, Trial named	Study design Setting Quality (Jadad Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in period/ Randomization Method Wash-out period/ Randomization Method	Allowed other medications	Method of outcome assessment Timing of assessment	Age mean/ Age range Gender Ethnicity
OCD and Depression Risperidone (Li X et al., 2005) US	Design: CCT, Crossover Setting: Single center Jadad: 2	Inclusion criteria: Y-BOCS ≥ 10 on items 1-5, Y-BOCS ≥ 16 Exclusion criteria: DSM-IV Axis I disorder, not including primary condition studied, SADS-L (Schedule for Affective Disorders and Schizophrenia - Lifetime version) Criteria, Major motor disorder, Vocal tics	Placebo - dosage not reported, Fluoxetine or Paroxitine = 40/mg/day, Fluvoxamine = 200 mg/day, or Sertraline = 100mg/day - therapeutic doses for at least 12 weeks Haloperidol - 2 mg/day fixed single dose, Fluoxetine or Paroxitine = 40/mg/day, Fluvoxamine = 200 mg/day, or Sertraline = 100mg/day - therapeutic doses for at least 12 weeks Risperidone - 1 mg/day fixed single dose, Fluoxetine or Paroxitine = 40/mg/day, Fluvoxamine = 200 mg/day, or Sertraline = 100mg/day - therapeutic doses for at leas Duration: 2.3 months	1 wk of placebo for randomization not described 1 wk of placebo for randomization not described	Antihistamine, Benztropine	Assessed at baseline and 2 weeks: YBOCS, SCL_90, HAM_D_HDRS, POMS, SNST, HVLT-R, CPT	34 / 19-56 44% male NR

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
Depression Olanzapine (Tohen M et al., 2002) US & Canada	501/344/344	94/8/334	Outcome of interested for statistical analysis not reported.	Monitored
Depression Quetiapine (Yargic LI et al., 2004) Turkey	NR/120/NR	17/NR/84	Depression_mood-Change in HAM-D at 8 weeks: Paroxetine vs Paroxetine + quetiapine-SMD = -0.223 (-0.595,0.149)	Elicited by investigator, reported by patient
OCD Quetiapine (Atmaca M et al., 2002) Turkey	52/27/27	0/0/27	OCD-Change in Y-BOCS at 8 weeks: SRI + placebo vs SRI + quetiapine-WMD = -8(-10.876, -5.124) OCD-Change in Number of Responders at 8 weeks: SRI + placebo vs SRI + quetiapine-RR = 19.6(1.263115, 304.1371) OCD_severity-Change in CGI-S at 8 weeks: SRI + placebo vs SRI + quetiapine-WMD = -1.34 (-2.209,-0.471)	Monitored, reported by patient

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
OCD Quetiapine (Denys D et al., 2004) Western Europe	NR/40/40	1/0/40	OCD-Change in Y-BOCS at 8 weeks: SRI + placebo vs SRI + quetiapine-WMD = -5.4 (-9.342,-1.458) OCD-Change in Number of Responders at 8 weeks: SRI + placebo vs SRI + quetiapine-RR = 4(0.9,16.5) OCD_improvement-Change in CGI-I at 8 weeks: SRI + placebo vs SRI + quetiapine-WMD = -0.85 (-1.411,-0.289)	Elicited by investigator, reported by patient, clinical observation and exam

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
OCD Risperidone (Cavedini P et al., 2004) Western Europe	NR/30/30	NR/NR/NR	OCD-Change in Y-BOCS at 12 weeks: Fluvoxamine + placebo (good IGT+) vs Fluvoxamine + risperidone (bad IGT)- WMD = -0.4 (-6.305,5.505) OCD-Change in Y-BOCS at 12 weeks: Fluvoxamine + placebo (bad IGT+) vs Fluvoxamine + risperidone (bad IGT)- WMD = -7.9 (-14.842,-0.958) OCD – Change in severity Fluv + placebo (good IGT) vs. Fluv + risperidone (bad IGT): RR=0.889, (0.612, 1.290) Fluv + placebo (bad IGT) vs. Fluv + risperidone (bad IGT): RR=8.0, (1.214, 52.692)	NR

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
OCD Risperidone (McDougle CJ et al., 2000) US	70/36/36	3/0/33	OCD-Change in Y-BOCS at 6 weeks: Placebo + SRI vs Risperidone + SRI-WMD = -6.29 (-10.777,-1.803) OCD-Change in Number of Responders at 6 weeks: Placebo + SRI vs Risperidone + SRI-RR = 16(1.0,254.1) OCD_improvement-Change in CGI-I at 6 weeks: Placebo + SRI vs Risperidone + SRI-WMD = -0.8 (-2.065,0.465)	Monitored
OCD and Tourettes Olanzapine (Shapira NA et al., 2004) US	74/44/44	4/3/1944	OCD-Change in Y-BOCS at 6 weeks: Fluoxetine + placebo vs Fluoxetine + olanzapine-WMD = -1.9(-5.033,1.233) OCD-Change in Number of Responders at 6 weeks: Fluoxetine + placebo vs Fluoxetine + olanzapine-RR = 1(0.5,2.0)	NR

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
Depression Ziprasidone (Dunner D et al., 2003) US	90/64/64	NR/NR/60	Depression_improvement-Change in CGI-I at 8 weeks: Sertraline vs Sertraline + Ziprasidone-WMD = -0.625(-1.006,-0.244) Depression_mood-Change in MADRS at 8 weeks: Sertraline vs Sertraline + Ziprasidone-SMD = -0.444(-0.807,-0.082) Depression_severity-Change in CGI-S at 8 weeks: Sertraline vs Sertraline + Ziprasidone-WMD = -0.62(-0.988,-0.252)	Monitored

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
OCD and Depression Quetiapine (Carey PD et al., 2005) Canada, South Africa ISRCTN83050762	NR/42/42	2/0/41	Depression_mood-Change in MADRS at 6 weeks: Placebo vs Quetiapine-SMD = 0.71(0.077,1.342) Depression_severity-Change in CGI-S at 6 weeks: Placebo vs Quetiapine-WMD = -3.61(-6.968,-0.252) OCD-Change in Y-BOCs at 6 weeks: Placebo vs Quetiapine-SMD = -0.146(-0.759,0.467) OCD-Change in Number of Responders at 6 weeks: Placebo vs Quetiapine-RR = 1.28(0.609,2.691)	Monitored

Condition, Drug Author, Year, Country, Trial named	Screened/Eligible/ Enrolled	Withdrawn/Lost to FU/ Analyzed	Results	Methods of adverse events assessment
OCD and Depression Quetiapine (Fineberg NA et al., 2005) UK	NR/21/21	4/0/21	Depression_mood-Change in MADRS at 16 weeks: Placebo vs Quetiapine-SMD = -1.06(-1.98,-0.14) Depression_severity-Change in CGI-S at 16 weeks: Placebo vs Quetiapine-WMD = -0.4(-1.302,0.502) OCD-Change in Y-BOCs at 16 weeks: Placebo vs Quetiapine-SMD = 0.615(-0.264,1.493) OCD-Change in Number of Responders at 16 weeks: Placebo vs Quetiapine-RR = 2.727(0.336,22.158)	Monitored
OCD and Depression Risperidone (Li X et al., 2005) US	27/16/16	NR/NR/NR	OCD Crossover study.	Monitored

Condition, Drug **Author, Year, Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
Depression Olanzapine (Tohen M et al., 2002) US & Canada	Lithium or valproate vs Olanzapine + (lithium or valproate): Asthenia: 13.0%(14.95/115) vs 18.3%(41.907/229) Depression: 17.4%(20.01/115) vs 17.9%(40.991/229) Diarrhea: 14.8%(17.02/115) vs 11.8%(27.022/229) Dizziness: 7.0%(8.05/115) vs 13.5%(30.915/229) Dry mouth: 7.8%(8.97/115) vs 31.9%(73.051/229) Headache: 18.3%(21.045/115) vs 15.7%(35.953/229) Increased appetite: 7.8%(8.97/115) vs 23.6%(54.044/229) Nervousness: 14.8%(17.02/115) vs 10.5%(24.045/229) Somnolence: 27.0%(31.05/115) vs 51.5%(117.935/229) Speech disorder: 0.9%(1.035/115) vs 6.6%(15.114/229) Thirst: 6.1%(7.015/115) vs 10.0%(22.9/229) Tremor: 13.0%(14.95/115) vs 23.1%(52.899/229) Weight gain: 7.0%(8.05/115) vs 26.2%(59.998/229) Weight change in kg: Monotherapy, Full Sample-115 people (0.23 mean,2.48 SD) vs Monotherapy, Lithium-41 people (Mean NR , SD NR) vs Monotherapy, Valproate-73 people (Mean NR , SD NR) vs Olanzapine Cotherapy, Full Sample-229 people (3.08 mean,3.04 SD) vs Olanzapine Cotherapy, Lithium-74 people (Mean NR , SD NR) vs Olanzapine Cotherapy, Valproate-145 people (Mean NR , SD NR)	Lithium or valproate vs Olanzapine + (lithium or valproate): Withdrawals: 28.7%(33/115) vs 30.1%(69/229) Withdrawals due to adverse events: 1.7%(2/115) vs 10.9%(25/229)
Depression Quetiapine (Yargic LI et al., 2004) Turkey	Paroxetine + quetiapine vs Paroxetine: Increased anxiety: 2.0%(1.16/58) vs 13.3%(7.182/54) Increased appetite: 20.4%(11.832/58) vs 2.4%(1.296/54) Insomnia: 0.0%(0/58) vs 31.0%(16.74/54)	Paroxetine + quetiapine vs Paroxetine: Withdrawals: 19.0%(11/58) vs 31.5%(17/54) Withdrawals due to adverse events: 3.4%(2/58) vs 16.7%(9/54)
OCD Quetiapine (Atmaca M et al., 2002) Turkey	SRI + placebo vs SRI + quetiapine: At least one adverse event: 30.8%(4/13) vs 64.3%(9/14) Dizziness: 0.0%(0/13) vs 7.1%(1/14) Headache: 7.7%(1/13) vs 0.0%(0/14) Nausea: 0.0%(0/13) vs 42.9%(6/14) Nervousness: 7.7%(1/13) vs 0.0%(0/14) Sedation: 15.4%(2/13) vs 21.4%(3/14) Weight change in kg: SRI + Placebo-13 people (1.6 mean,1.3 SD) vs SRI + Quetiapine-14 people (1.9 mean,1.8 SD)	SRI + placebo vs SRI + quetiapine: Withdrawals: 0.0%(0/13) vs 0.0%(0/14) Withdrawals due to adverse events: 0.0%(0/13) vs 0.0%(0/14)

Condition, Drug **Author, Year, Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
OCD Quetiapine (Denys D et al., 2004) Western Europe	SRI + placebo vs SRI + quetiapine: At least 2 or 3 adverse events: 100.0%(20/20) vs 100.0%(20/20) Asthenia: 0.0%(0/20) vs 10.0%(2/20) Change in mood: 15.0%(3/20) vs 10.0%(2/20) Diarrhea: 10.0%(2/20) vs 0.0%(0/20) Dizziness: 0.0%(0/20) vs 30.0%(6/20) Dry mouth: 40.0%(8/20) vs 55.0%(11/20) Increased appetite: 0.0%(0/20) vs 20.0%(4/20) Muscular pain: 0.0%(0/20) vs 10.0%(2/20) Nightmares: 0.0%(0/20) vs 10.0%(2/20) Palpitations: 10.0%(2/20) vs 0.0%(0/20) Problems with concentration: 0.0%(0/20) vs 15.0%(3/20) Somnolence: 35.0%(7/20) vs 95.0%(19/20) Sweating: 30.0%(6/20) vs 10.0%(2/20) Weight gain: 0.0%(0/20) vs 30.0%(6/20)	SRI + placebo vs SRI + quetiapine: Withdrawals: 0.0%(0/20) vs 5.0%(1/20) Withdrawals due to adverse events: 0.0%(0/20) vs 0.0%(0/20)
OCD Risperidone (Cavedini P et al., 2004) Western Europe	No adverse events reported.	Fluvoxamine + Placebo vs Fluvoxamine + Placebo vs Fluvoxamine + Risperidone: Withdrawals: Not reported Withdrawals due to adverse events: Not reported
OCD Risperidone (McDougle CJ et al., 2000) US	Placebo + SRI vs Risperidone + SRI: At least one adverse event: 100.0%(15/16) vs 90.0%(18/20) Blurred vision: 12.5%(2/16) vs 0.0%(0/20) Constipation: 0.0%(0/16) vs 5.0%(1/20) Diaphoresis: 25.0%(4/16) vs 5.0%(1/20) Diarrhea: 6.3%(1/16) vs 0.0%(0/20) Dry mouth: 31.3%(5/16) vs 25.0%(5/20) Headache: 31.3%(5/16) vs 0.0%(0/20) Increased appetite: 18.8%(3/16) vs 30.0%(6/20) Insomnia: 6.3%(1/16) vs 5.0%(1/20) Lightheadedness: 25.0%(4/16) vs 5.0%(1/20) Muscle stiffness: 6.3%(1/16) vs 0.0%(0/20) Palpitations: 6.3%(1/16) vs 0.0%(0/20) Restlessness: 37.5%(6/16) vs 30.0%(6/20) Sedation: 50.0%(8/16) vs 85.0%(17/20) Tinnitus: 6.3%(1/16) vs 10.0%(2/20) Urinary urgency: 0.0%(0/16) vs 5.0%(1/20)	Placebo + SRI vs Risperidone + SRI: Withdrawals: 6.3%(1/16) vs 10.0%(2/20) Withdrawals due to adverse events: 0.0%(0/16) vs 5.0%(1/20)

Condition, Drug **Author, Year, Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
OCD and Tourettes Olanzapine (Shapira NA et al., 2004) US	No adverse events reported. Weight change in kg: Fluoxetine + placebo-22 people (0.5 mean,1.8 SD) vs Fluoxetine + Olanzapine-22 people (2.8 mean,3.1 SD)	Fluoxetine + Placebo vs Fluoxetine + Olanzapine: Withdrawals: 9.1%(2/22) vs 22.7%(5/22) Withdrawals due to adverse events: 9.1%(2/22) vs 9.1%(2/22)
Depression Ziprasidone (Dunner D et al., 2003) US	Sertraline vs Ziprasidone: Abnormal ejaculation: 5.0%(1/21) vs 0.0%(0/43) Abnormal thinking: 0.0%(0/21) vs 9.3%(4/43) Abnormal vision: 0.0%(0/21) vs 11.6%(5/43) Agitation: 0.0%(0/21) vs 20.9%(9/43) Anxiety: 10.0%(2/21) vs 0.0%(0/43) Asthenia: 0.0%(0/21) vs 20.9%(9/43) Back pain: 0.0%(0/21) vs 4.7%(2/43) Constipation: 0.0%(0/21) vs 9.3%(4/43) Dizziness: 0.0%(0/21) vs 18.6%(8/43) Dry Mouth: 0.0%(0/21) vs 14.0%(6/43) Headache: 5.0%(1/21) vs 16.3%(7/43) Insomnia: 5.0%(1/21) vs 30.2%(13/43) Nausea: 0.0%(0/21) vs 11.6%(5/43) Neck pain: 0.0%(0/21) vs 4.7%(2/43) Respiratory tract infection: 0.0%(0/21) vs 11.6%(5/43) Somnolence: 10.0%(2/21) vs 18.6%(8/43) Tooth disorder: 0.0%(0/21) vs 7.0%(3/43) Tremor: 5.0%(1/21) vs 16.3%(7/43)	Sertraline vs Ziprasidone: Withdrawals: (NR/21) vs (NR/43) Withdrawals due to adverse events: (NR/21) vs (NR/43)
OCD and Depression Quetiapine (Carey PD et al., 2005) Canada, South Africa ISRCTN83050762	Placebo vs Quetiapine: Abdominal tenderness: 0.0%(0/21) vs 5.0%(1/21) Delayed ejaculation: 0.0%(0/21) vs 5.0%(1/21) Dizziness: 14.3%(3/21) vs 5.0%(1/21) Dry Mouth: 0.0%(0/21) vs 15.0%(3/21) Fatigue: 19.0%(4/21) vs 15.0%(3/21) Headache: 38.0%(8/21) vs 15.0%(3/21) Impared concentration: 0.0%(0/21) vs 10.0%(2/21) Increased appetite: 9.5%(2/21) vs 5.0%(1/21) Irritability: 4.7%(1/21) vs 10.0%(2/21) Memory difficulties: 0.0%(0/21) vs 5.0%(1/21) Muscle aches: 0.0%(0/21) vs 5.0%(1/21) Nausea: 9.5%(2/21) vs 5.0%(1/21) Sedation: 33.3%(7/21) vs 75.0%(15/21) Slurred speech: 0.0%(0/21) vs 5.0%(1/21) Weight gain: 0.0%(0/21) vs 5.0%(1/21) Worsening mood: 4.7%(1/21) vs 5.0%(1/21)	Placebo vs Quetiapine: Withdrawals: 0.0%(0/21) vs 9.5%(2/21) Withdrawals due to adverse events: 0.0%(0/21) vs 9.5%(2/21)

Condition, Drug **Author, Year, Country, Trial named**	**Adverse events reported**	**Total withdrawals** **Withdrawals due to adverse events**
OCD and Depression Quetiapine (Fineberg NA et al., 2005) UK	Placebo vs Quetiapine: Drowsiness: (NR/10) vs 72.7%(8/11) Dry Mouth: (NR/10) vs 54.5%(6/11) Fatigue: (NR/10) vs 9.1%(1/11) Headache: (NR/10) vs 54.5%(6/11) Restless limbs: (NR/10) vs 36.4%(4/11) Stiffness: (NR/10) vs 45.5%(5/11)	Placebo vs Quetiapine: Withdrawals: 10.0%(1/10) vs 27.3%(3/11) Withdrawals due to adverse events: 0.0%(0/10) vs 9.1%(1/11)
OCD and Depression Risperidone (Li X et al., 2005) US	Adverse events not reported before crossover.	Placebo vs Placebo vs Haloperidol vs Haloperidol vs Risperidone vs Risperidone: Withdrawals: (NR/6) vs (NR/6) vs (NR/5) vs (NR/5) vs (NR/5) vs (NR/5) Withdrawals due to adverse events: (NR/6) vs (NR/6) vs (NR/5) vs (NR/5) vs (NR/5) vs (NR/5)

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
ADL	Activities of Daily Life
AIAQ	Anger, Irritability, and Assault Questionnaire
ASI	Addiction Severity Index
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Index
BDHI	Buss-Durkee Hostility Index
BDI	Beck Depression Index
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelsen Melancholia Scale
CAPS	Clinician Administered PTSD Scale
CDSS	Calgary Depression Scale for Schizophrenia
CES-D	Center for Epidemiologic Studies Depression Scale
CGI	Clinical Global Impression Scale
CMAI	Cohen-Mansfield Agitation Inventory
CM-PNB	Cohen-Mansfield Physically Non-Aggressive Behavior
CPRS	Children's Psychiatric Rating Scale
CSDD	Cornell Scale for Depression in Dementia
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DCM	Dementia Care Mapping
DES	Dissociative Experiences Scale
DTS	Davidson Trauma Scale
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
FAST	Functional Assessment Staging Rating Scale
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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C5: Quality Tables – Head to Head Trials

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/high
(Fontaine CS et al., 2003)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Herz LR et al., 2002)	Yes	Yes	NR	Yes	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Mullen J et al., 2001)	Method NR	Method NR	Yes	Yes	No	No	No	Yes/NR /NR /NR	No
(Deberdt WG et al., 2005)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Levitt A et al., 2004)	Method NR	Method NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes, but not described	NR /NR /NR /NR	NR
(Mulsant BH et al., 2004)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Tollefson GD et al., 1999)	Method NR	Method NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	No
(Kinon BJ et al., 2005)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Simpson GM et al., 2004)	Method NR	Method NR	Yes	Yes	NR	Yes	Yes	Yes/NR /NR /NR	NR

Study	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/Eligible/ Enrolled	Exclusion criteria
(Fontaine CS et al., 2003)	Yes	No	3	NR/47/39	Neuroleptic malignant syndrome, Atypical antipsychotics sensitivity, Major depressive disorder, Schizophrenia, Bipolar disorder, Antihypertensive drug treatment, Antibiotic treatment, Antiparkinsonian drug treatment
(Herz LR et al., 2002)	Yes	No	3	NR/29/29	NR
(Mullen J et al., 2001)	No	No	1	NR/728/728	Under 18 years old, Medically significant disorders, Clozapine treatment, Clozapine unresponsiveness, Previous drug-induced agranulocytosis, Pregnant, Lactating, Participation in previous quetiapine trial, Participation in previous clinical trial within 4 months, Risperidone treatment within 4 months
(Deberdt WG et al., 2005)	Yes	No	2	NR/494/494	Frontotemporal dementia, Lewy body dementia, MMSE > 24, Parkinsons disease, Picks disease
(Levitt A et al., 2004)	Yes	No	3	NR/43/43	Suicidal, current Axis 1 DSM IV diagnosis other than anxiety disorder, substance abuse in past 3 months, pregnant, lactating or certain other medications
(Mulsant BH et al., 2004)	Yes	No	2	NR/86/86	Psychosis before dementia onset, Delirium, Inability to swallow oral medication or unable to cooperate with study
(Tollefson GD et al., 1999)	No	No	2	NR/339/339	NR
(Kinon BJ et al., 2005)	No	No	2	NR/394/NR	Previous sensitivity or unresponsiveness to stuffy drug
(Simpson GM et al., 2004)	Yes	No	4	367/269/269	Pregnant, Hospitalized ≥ 2 wks, Abnormal laboratory results, DSM-IV Axis I disorder, not including primary condition studied, Depot neuroleptic within 1 treatment cycle, Resistant to antipsychotic treatment, Suicidal or violent, Olanzapine > 14 days life time exposure or olanzapine daily dose >10 m

Study	Run-in/Randomization Method Washout/Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Fontaine CS et al., 2003)	NR Washout period reported	No	Yes	Source: Industry Role: described	Yes
(Herz LR et al., 2002)	NR NR	NR	No - Placebo	Source: NR Role: NR	Yes
(Mullen J et al., 2001)	NR NR	No	Yes	Source: Industry Role: NR	Yes
(Deberdt WG et al., 2005)	NR Washout period reported	NR	Yes	Source: Industry Role: NR	Yes
(Levitt A et al., 2004)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Mulsant BH et al., 2004)	Run-in period reported Washout period reported	NR	Yes	Source: Industry Role: described	Yes
(Tollefson GD et al., 1999)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Kinon BJ et al., 2005)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Simpson GM et al., 2004)	NR Washout period reported	NR	Yes	Source: Industry Role: NR	Yes

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lbs	pounds
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NOS	Not otherwise specified
NR	Not reported
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Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
ADL	Activities of Daily Life
AIAQ	Anger, Irritability, and Assault Questionnaire
ASI	Addiction Severity Index
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Index
BDHI	Buss-Durkee Hostility Index
BDI	Beck Depression Index
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelsen Melancholia Scale
CAPS	Clinician Administered PTSD Scale
CDSS	Calgary Depression Scale for Schizophrenia
CES-D	Center for Epidemiologic Studies Depression Scale
CGI	Clinical Global Impression Scale
CMAI	Cohen-Mansfield Agitation Inventory
CM-PNB	Cohen-Mansfield Physically Non-Aggressive Behavior
CPRS	Children's Psychiatric Rating Scale
CSDD	Cornell Scale for Depression in Dementia
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DCM	Dementia Care Mapping
DES	Dissociative Experiences Scale
DTS	Davidson Trauma Scale
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FAST	Functional Assessment Staging Rating Scale
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
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NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
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SANS	Scale for the Assessment of Negative Symptoms
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SIP	Structured Interview for PTSD
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C6: Quality Tables - Active Control Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
(Malone RP et al., 2001)	Yes	Method NR	Yes	Yes	No
(Meehan KM et al., 2002)	Method NR	Method NR	Yes	Yes	NR
(Ballard C et al., 2005)	Yes	Yes	Yes	Yes	Yes
(Chan WC et al., 2001)	Method NR	Method NR	Yes	Yes	NR
(De Deyn PP et al., 1999)	Yes	Yes	Yes	Yes	NR
(Suh GH et al., 2004)	Method NR	Yes	Yes	Yes	NR
(David S JBAKWP, 2002)	Method NR	Method NR	NR	NR	NR
(McEvoy J et al.,)	Method NR	Method NR	Yes	Yes	NR
(Shelton RC et al., 2001)	Method NR	Method NR	NR	Yes	Yes, but not described
(Street JS et al., 2000)	Not randomized	Not randomized	NR	Yes	NR
(Svestka J SO, 2000)	Method NR	Method NR	NR	Yes	NR
(Tohen M et al., 1999)	Method NR	Method NR	NR	Yes	NR
(Tohen M et al., 2002)	Method NR	Method NR	Yes	Yes	Yes
(Tohen M et al., 2005)	Method NR	Method NR	Yes	Yes	Yes
(Tollefson GD et al., 1997)	Yes	Method NR	Yes	Yes	NR
(Gareri P et al., 2004)	Method NR	Method NR	NR	Yes	Yes
(Altamura AC et al., 2003)	Method NR	Method NR	Yes	Yes	Yes
(Muller-Siecheneder F et al., 1998)	Method NR	Method NR	Yes	Yes	Yes, but not described
(Shelton RC et al., 2004)	Method NR	Method NR	Yes	Yes	NR

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
(Weiser M et al., 2002)	Method NR	Method NR	Yes	Yes	No
(Zanarini MC et al., 2004)	Method NR	Method NR	Yes	Yes	Yes, but not described
(Bruggeman R et al., 2001)	Yes	Yes	Yes	Yes	NR
(Gaffney GR et al., 2002)	Method NR	Method NR	Yes	Yes	NR
(Kinon BJ et al., 2005)	Method NR	Method NR	Yes	Yes	Yes, but not described
(Kasper S et al., 2003)	Method NR	Method NR	Yes	Yes	NR
(Corya SA et al., 2005)	Method NR	Method NR	NR	Yes	NR
(Dunner DL et al., 2005)	Method NR	Method NR	Yes	Yes	NR
(Shelton RC et al., 2005)	Method NR	Method NR	Yes	Yes	NR
(Gilbert DL et al., 2004)	Yes	Yes	NR	Yes	NR

Author, Year	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/high
(Malone RP et al., 2001)	No	No	Yes/NR /NR /NR	No
(Meehan KM et al., 2002)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Ballard C et al., 2005)	Yes	Yes	Yes/NR /NR /NR	No
(Chan WC et al., 2001)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(De Deyn PP et al., 1999)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Suh GH et al., 2004)	Yes	Yes	Yes/NR /NR /NR	No
(David S JBAKWP, 2002)	No	No	NR /NR /NR /NR	NR
(McEvoy J et al.,)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Shelton RC et al., 2001)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Street JS et al., 2000)	NR	NR	NR /NR /NR /NR	NR
(Svestka J SO, 2000)	Yes, but not described	Yes, but not described	NR /NR /NR /NR	No
(Tohen M et al., 1999)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Tohen M et al., 2002)	Yes	Yes	Yes/NR /NR /NR	No
(Tohen M et al., 2005)	Yes	Yes	Yes/NR /Yes/NR	No
(Tollefson GD et al., 1997)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Gareri P et al., 2004)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Altamura AC et al., 2003)	No	No	NR /NR /NR /NR	No
(Muller-Siecheneder F et al., 1998)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Shelton RC et al., 2004)	Yes	Yes	Yes/NR /NR /NR	No
(Weiser M et al., 2002)	No	No	Yes/NR /NR /NR	NR

Author, Year	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/high
(Zanarini MC et al., 2004)	NR	Yes, but not described	Yes/NR /NR /NR	No
(Bruggeman R et al., 2001)	Yes	Yes	Yes/NR /NR /NR	No
(Gaffney GR et al., 2002)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Kinon BJ et al., 2005)	No	No	Yes/NR /Yes/NR	No
(Kasper S et al., 2003)	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	NR
(Corya SA et al., 2005)	Yes	Yes	Yes/NR /Yes/NR	No
(Dunner DL et al., 2005)	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	Yes
(Shelton RC et al., 2005)	Yes	Yes	Yes/NR /Yes/NR	No
(Gilbert DL et al., 2004)	Yes, but not described	Yes, but not described	Yes/Yes/NR /NR	No

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/Enrolled	Exclusion criteria
(Malone RP et al., 2001)	Yes	No	3	NR/13/12	Medically significant disorders, Seizure disorder or epilepsy or risk, Neurological disorder, Psychotropic medications, Previous exposure to study drug
(Meehan KM et al., 2002)	No	No	2	331/272/272	Anticholinergic medications, Antipsychotic medications, Benzodiazepines, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, Abnormal laboratory results, Suicidal or violent
(Ballard C et al., 2005)	Yes	No	4	282/93/93	Antipsychotics treatment≥4 wks, Cholinesterase treatment≥4 wks, Previous sensitivity or unresponsiveness to stuffy drug, Severe internal or neurological disease, Medically significant disorders
(Chan WC et al., 2001)	Yes	No	3	NR/58/58	Lewy body dementia, Neurological or medical conditions diminishing cognitive function, Psychosis/psychotic features, Medically significant disorders, Abnormal laboratory results, Allergic or toxic reactions to psychotropic medications, Neuroleptic malignant syndrome
(De Deyn PP et al., 1999)	No	No	4	371/344/344	Neurological or medical conditions diminishing cognitive function, Other psychiatric disorders, Severe internal or neurological disease, Abnormal laboratory results, Depot neuroleptic within 1 treatment cycle, Allergic or toxic reactions to psychotropic medication, Participation in a clinical trial with investigational drugs during the 4 weeks preceding this trial, Other psychotropics, psychotropic herbs, history of non-affective disorder.

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/Enrolled	Exclusion criteria
(Suh GH et al., 2004)	Yes	No	4	280/120/120	Neurological or medical conditions diminishing cognitive function, Psychotic disorder, Severe internal or neurological disease, Medically significant disorders, Abnormal laboratory results, Allergic or toxic reactions to antipsychotic medications, Neuroleptic malignant syndrome
(David S JBAKWP, 2002)	No	Unable to determine	2	NR/1054/NR	NR
(McEvoy J et al.,)	Yes	No	2	NR/263/263	Pregnant, Clozapine treatment, Antipsychotic treatment > 16 wks in a lifetime, Lactating, Medically significant disorders, Previous sensitivity or unresponsiveness to stuffy drug, Alcohol or substance abuse or dependency, Suicidal or violent
(Shelton RC et al., 2001)	Yes	No	2	34/33/28	Psychosis/psychotic features, Dysthymic disorder, Bipolar disorder
(Street JS et al., 2000)	No	Unable to determine	1	NR/NR/NR	NR
(Svestka J SO, 2000)	Yes	No	3	NR/40/40	NR
(Tohen M et al., 1999)	No	No	2	NR/28/NR	NR
(Tohen M et al., 2002)	Yes	No	3	330/251/251	Medically significant disorders, Alcohol or substance abuse or dependency, Atypical antipsychotics sensitivity, Sensitivity to mood stabilizer, Treatment with lithium, anticonvulsant, or antipsychotic within 24 hrs
(Tohen M et al., 2005)	Yes	No	4	543/431/431	Medically significant disorders, Alcohol or substance abuse or dependency, Depot neuroleptic within 6 weeks, Suicidal or violent, Previous sensitivity or unresponsiveness to stuffy drug
(Tollefson GD et al., 1997)	Yes	No	5	2223/1996/1996	NR
(Gareri P et al., 2004)	Yes	No	3	NR/60/60	NR
(Altamura AC et al., 2003)	Yes	No	2	NR/28/28	Abnormal laboratory results, HIV dementia
(Muller-Siecheneder F et al., 1998)	Yes	No	4	NR/123/123	Suicidal or violent, Severe internal or neurological disease, Abnormal laboratory results, Allergic or toxic reactions to psychotropic medications, Participation in previous clinical trial within 4 months, Pregnant, Lactating

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/Enrolled	Exclusion criteria
(Shelton RC et al., 2004)	Yes	No	4	NR/30/30	Current psychosis, Alcohol or substance abuse or dependency, Other psychotropics, psychotropic herbs, history of non-affective disorder
(Weiser M et al., 2002)	Yes	No	1	NR/90/85	NR
(Zanarini MC et al., 2004)	Yes	No	2	NR/45/45	Fluoxetine successful treatment, Olanzapine successful treatment, Medically significant disorders, Seizure disorder or epilepsy or risk, Psychotropic medications, Alcohol or substance abuse or dependency, Suicidal or violent, Major depressive disorder
(Bruggeman R et al., 2001)	Yes	Yes	5	NR/51/51	NR
(Gaffney GR et al., 2002)	Yes	No	3	24/21/21	Seizure disorder or epilepsy or risk, Neurological disorder, Pregnant, Abnormal laboratory results
(Kinon BJ et al., 2005)	Yes	No	2	NR/293/293	Tardive dyskinesia
(Kasper S et al., 2003)	Yes	No	2	NR/1294/1294	Pregnant, Lactating, Resistant to antipsychotic treatment, Suicidal or violent, Alcohol or substance abuse or dependency, Neurological disorder, Investigational drug use≥4 wks, Psychiatric disorder, not including primary conditioned studied
(Corya SA et al., 2005)	Yes	No	3	807/483/483	Bipolar disorder, Psychotic disorder, Schizophrenia, Schizoaffective disorder, PTSD, Major depressive disorder with seasonal pattern, Dissociative disorder
(Dunner DL et al., 2005)	Yes	No	2	NR/410/410	Suicidal or violent, Alcohol or substance abuse or dependency, Previous exposure to study drug, Previous failure or responded poorly to olanzapine, antidepressants or lamotrigine, Olanzapine + antidepressants treatment, Lamotrigine treatment, YMRS≥15
(Shelton RC et al., 2005)	Yes	No	3	946/500/500	BPRS positive item score≥3, Pregnant, Lactating, ECT treatment history or requiring during study

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/Enrolled	Exclusion criteria
(Gilbert DL et al., 2004)	Yes	No	5	NR/19/19	Psychotic disorder, Alcohol or substance abuse or dependency, Pervasive developmental disorder, Eating disorders, Transient tic disorder, Medically significant disorders, Abnormal laboratory results, Sexually active females of child bearing age not using an effective contraceptive method

Author, Year	Run-in/Randomization Method Washout/Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Malone RP et al., 2001)	NR NR	NR	Yes	Source: Industry Role: described	Yes
(Meehan KM et al., 2002)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(Ballard C et al., 2005)	NR NR	NR	No - Placebo	Source: Industry & Private Role: described	Yes
(Chan WC et al., 2001)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(De Deyn PP et al., 1999)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Suh GH et al., 2004)	NR Washout period reported	NR	Yes	Source: Industry Role: described	Yes
(David S JBAKWP, 2002)	NR NR	NR	No - Placebo	Source: NR Role: NR	Yes
(McEvoy J et al.,)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Shelton RC et al., 2001)	NR NR	NR	No - Fluoxetine (for nonresponders)	Source: Government & Industry Role: NR	Yes
(Street JS et al., 2000)	NR NR	NR	NR	Source: Industry Role: NR	Yes
(Svestka J SO, 2000)	Run-in period reported NR	NR	No - Amitriptyline	Source: NR Role: NR	Yes
(Tohen M et al., 1999)	Run-in period reported NR	NR	NR	Source: NR Role: NR	Yes
(Tohen M et al., 2002)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Tohen M et al., 2005)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Tollefson GD et al., 1997)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Gareri P et al., 2004)	NR Washout period reported	NR	Yes	Source: Government Role: NR	Yes
(Altamura AC et al., 2003)	NR NR	NR	Yes	Source: NR Role: NR	Yes
(Muller-Siecheneder F et al., 1998)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Shelton RC et al., 2004)	NR NR	NR	Yes	Source: Government & Industry Role: described	Yes
(Weiser M et al., 2002)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Zanarini MC et al., 2004)	NR NR	NR	NR	Source: Industry Role: NR	Yes

Author, Year	Run-in/Randomization Method Washout/Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Bruggeman R et al., 2001)	NR Washout period reported	NR	Yes	Source: Industry Role: described	Yes
(Gaffney GR et al., 2002)	Run-in period reported Washout period reported	NR	Yes	Source: Industry & Private Role: NR	Yes
(Kinon BJ et al., 2005)	Run-in period reported NR	No	Yes	Source: Industry Role: NR	Yes
(Kasper S et al., 2003)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Corya SA et al., 2005)	Run-in period reported NR	No	Yes	Source: Industry Role: NR	Yes
(Dunner DL et al., 2005)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Shelton RC et al., 2005)	Run-in period reported Washout period reported	No	Yes	Source: Industry Role: described	Yes
(Gilbert DL et al., 2004)	Run-in period reported Washout period reported	No	Yes	Source: Government & Industry Role: NR	Yes

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
ADHDRS	DuPaul Attention Deficit Hyperactivity Scale
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HAM-D/HDRS	Hamilton Rating Scale for Depression
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MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
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MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
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NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
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NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
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SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
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STAS-AX	State-Trait Anger Expression Inventory
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YMRS	Young Mania Rating Scale

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C7: Quality Tables – Placebo Control Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
(McCracken JT et al., 2002)	Yes	Yes	Yes, except on ABC in appropriate speech score	Yes
(Shea S et al., 2004)	Yes	Yes	Yes	Yes
(De Deyn PP et al., 2004)	Method NR	Method NR	Yes	Yes
(Street JS et al., 2000)	Yes	Method NR	Yes	Yes
(Ruths S et al., 2004)	Method NR	Yes	NR	Yes
(Zhong X et al., 2004)	Method NR	Method NR	Yes	NR
(Ballard CG et al., 2004)	Method NR	Method NR	Yes	Yes
(Brodaty H et al., 2003)	Yes	Method NR	Yes	Yes
(Katz IR et al., 1999)	Method NR	Yes	Yes	Yes
(Meguro K et al., 2004)	Method NR	Method NR	Yes	Yes
(Mertens C, 1993)	Not randomized	Not randomized	Yes	Yes
(Corya S et al., 2002)	Method NR	Method NR	NR	NR
(Howanitz E et al., 2001)	Method NR	Method NR	NR	NR
(Kinrys G et al., 2002)	Method NR	Method NR	NR	Yes
(Rothschild AJ et al., 2004)	Method NR	Method NR	Yes	Yes
(Shi L et al., 2004)	Method NR	Yes	Yes	Yes
(Street JS et al., 2000)	Not randomized	Not randomized	NR	Yes
(Tohen M et al., 2003)	Method NR	Yes	Yes	Yes
(Tohen M et al., 2000)	Yes	Method NR	Yes	Yes

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
(Tohen M et al., 1999)	Method NR	Method NR	Yes	Yes
(Tohen M et al., 2003)	Method NR	Method NR	NR	Yes
(Tollefson GD et al., 1999)	Method NR	Method NR	Yes	Yes
(van Reekum R et al., 2002)	Yes	Method NR	NR	Yes
(Calabrese J et al., 2004)	Method NR	Method NR	Yes	Yes
(Mintzer J et al., 2004)	Method NR	Method NR	Yes	Yes
(Gharabawi GM et al., 2004)	Yes	Method NR	Yes	Yes
(Daniels DG et al., 1999)	Method NR	Method NR	Yes	Yes
(Keck P Jr et al., 1998)	Method NR	Method NR	Yes	Yes
(Bartzokis G et al., 2004)	Method NR	Method NR	Yes	Yes
(Padala PR et al., 2005)	Method NR	Method NR	NR	Yes
(Reich DB et al., 2004)	Method NR	Method NR	Yes	Yes
(Bystritsky A et al., 2004)	Method NR	Method NR	Yes	Yes
(Buchsbaum MS, 2003)	Not randomized	Not randomized	NR	Yes
(Erzegovesi S et al., 2005)	Yes	Yes	Yes	Yes
(Hollander E et al., 2003)	Yes	Method NR	Yes	Yes
(Butterfield MI et al., 2001)	Method NR	Method NR	Yes	Yes
(Stein MB et al., 2002)	Method NR	Method NR	Yes	Yes
(Hamner MB et al., 2003)	Yes	Method NR	Yes	Yes
(Monnelly EP et al., 2003)	Yes	Method NR	Yes	Yes

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
(Bogenschutz MP et al., 2004)	Method NR	Method NR	Yes	Yes
(Zanarini MC et al., 2001)	Yes	Method NR	Yes	Yes
(Koenigsberg HW et al., 2003)	Method NR	Method NR	Yes	Yes
(Sallee FR et al., 2000)	Method NR	Method NR	Yes	Yes
(Breder C et al., 2004)	Method NR	Method NR	Yes	Yes
(De Deyn P et al., 2005)	Method NR	Method NR	Yes	Yes
(Streim JE et al., 2004)	Method NR	Method NR	Yes	Yes
(McQuade R et al., 2004)	Method NR	Method NR	NR	Yes
(Kennedy J et al., 2005)	Method NR	Method NR	Yes	Yes
(Soler J et al., 2005)	Method NR	Method NR	Yes	Yes
(Scahill L et al., 2003)	Method NR	Method NR	NR	Yes

Author, Year	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/ high
(McCracken JT et al., 2002)	Yes	Yes	Yes, but not described	Yes/NR / Yes /NR	No
(Shea S et al., 2004)	No	No	No	Yes/NR / Yes /NR	No
(De Deyn PP et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	NR
(Street JS et al., 2000)	NR	Yes	Yes	Yes/NR /NR /NR	No
(Ruths S et al., 2004)	Yes	Yes	Yes	NR /NR /NR /NR	No
(Zhong X et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Ballard CG et al., 2004)	Yes	Yes	Yes	Yes/NR /NR /NR	No
(Brodaty H et al., 2003)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Katz IR et al., 1999)	NR	Yes	Yes	Yes/NR /NR /NR	No
(Meguro K et al., 2004)	NR	NR	NR	NR /NR /NR /NR	NR
(Mertens C, 1993)	NR	Yes	Yes	Yes/NR /NR /NR	No
(Corya S et al., 2002)	NR	Yes, but not described	Yes, but not described	NR /NR /NR /NR	NR
(Howanitz E et al., 2001)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Kinrys G et al., 2002)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Rothschild AJ et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	NR
(Shi L et al., 2004)	Yes	Yes	Yes	Yes/NR /NR /NR	No
(Street JS et al., 2000)	NR	NR	NR	NR /NR /NR /NR	NR
(Tohen M et al., 2003)	Yes	Yes	Yes	Yes/NR /NR /NR	No
(Tohen M et al., 2000)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No

Author, Year	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/ high
(Tohen M et al., 1999)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Tohen M et al., 2003)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Tollefson GD et al., 1999)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(van Reekum R et al., 2002)	NR	Yes	Yes	Yes/NR /NR /NR	No
(Calabrese J et al., 2004)	NR	Yes, but not described	Yes, but not described	NR /NR /NR /NR	NR
(Mintzer J et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Gharabawi GM et al., 2004)	Yes, but not described	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	No
(Daniels DG et al., 1999)	NR	Yes, but not described	Yes, but not described	NR /NR /NR /NR	NR
(Keck P Jr et al., 1998)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Bartzokis G et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	No
(Padala PR et al., 2005)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Reich DB et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Bystritsky A et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Buchsbaum MS, 2003)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Erzegovesi S et al., 2005)	Yes, but not described	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Hollander E et al., 2003)	Yes	Yes	Yes	Yes/NR /NR /NR	No
(Butterfield MI et al., 2001)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Stein MB et al., 2002)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Hamner MB et al., 2003)	NR	Yes	Yes	Yes/NR /NR /NR	No

Author, Year	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/ high
(Monnelly EP et al., 2003)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Bogenschutz MP et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Zanarini MC et al., 2001)	NR	Yes	Yes	Yes/NR /NR /NR	Yes
(Koenigsberg HW et al., 2003)	Yes, but not described	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Sallee FR et al., 2000)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Breder C et al., 2004)	NR	No	No	Yes/NR /NR /NR	NR
(De Deyn P et al., 2005)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	No
(Streim JE et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(McQuade R et al., 2004)	NR	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Kennedy J et al., 2005)	NR	Yes, but not described	Yes, but not described	Yes/NR /Yes/NR	No
(Soler J et al., 2005)	Yes, but not described	Yes, but not described	Yes, but not described	Yes/NR /NR /NR	NR
(Scahill L et al., 2003)	Yes	Yes	Yes	Yes/NR /NR /NR	No

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/ Enrolled	Exclusion criteria
(McCracken JT et al., 2002)	Yes	Yes	4	270/104/104	Medically significant disorders, DSM-IV Axis I disorder, not including primary condition studied, Psychotropic medication for behavioral disturbances
(Shea S et al., 2004)	Yes	Yes	5	NR/80/79	Schizophrenia or other psychotic disorder, Risperidone use in last 3 mos, Previously unresponsive or intolerant to Risperidone, Medically significant disorders, Abnormal laboratory results, Seizure disorder, Allergic or toxic reactions to antipsychotic medications, HIV, Tardive dyskinesia, Neuroleptic malignant syndrome, Alcohol or substance abuse
(De Deyn PP et al., 2004)	No	No	2	NR/652/NR	DSM-IV Axis I disorder, not including primary condition studied
(Street JS et al., 2000)	Yes	No	5	288/206/206	DSM-IV Axis I disorder, not including primary condition studied, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, MMSE > 24, Bedridden, Anticholinergic medications, Mood stabilizers, Antipsychotics other than the ones studied, Tricyclic antidepressants
(Ruths S et al., 2004)	Yes	No	4	51/30/30	Psychotic disorder, Mental retardation, Terminal illness, Recent major changes in health status
(Zhong X et al., 2004)	No	No	2	NR/333/NR	NR
(Ballard CG et al., 2004)	No	No	3	NR/100/100	NPI > 7
(Brodaty H et al., 2003)	Yes	No	3	384/345/345	Neurological or medical conditions diminishing cognitive function, Dementia other than primary condition, Major depressive disorder, Psychotic disorder, Tardive dyskinesia, Medically significant disorders, Abnormal laboratory results, Depot neuroleptic within 2 treatment cycles
(Katz IR et al., 1999)	Yes	No	4	729/625/625	Untreated reversible causes of dementia, Neurological or medical conditions diminishing cognitive function, HIV dementia, Substance induced dementia, Delirium, Amnestic disorder, Psychosis/psychotic features
(Meguro K et al., 2004)	No	No	1	NR/34/34	Cerebrovascular disease, Parkinsons disease
(Mertens C, 1993)	Yes	No	3	NR/39/39	Neurological or medical conditions diminishing cognitive function, Neurologic disorder, not including primary conditioned studied, Psychiatric disorder, not including primary conditioned studied
(Corya S et al., 2002)	No	No	2	NR/249/NR	NR
(Howanitz E et al., 2001)	Yes	No	2	NR/16/16	NR
(Kinrys G et al., 2002)	Yes	No	3	NR/14/14	NR

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/ Enrolled	Exclusion criteria
(Rothschild AJ et al., 2004)	Yes	No	2	NR/124/124	Psychotic disorder, Pregnant, Lactating
(Shi L et al., 2004)	Yes	No	3	1072/833/833	Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders
(Street JS et al., 2000)	No	Unable to determine	1	NR/NR/NR	NR
(Tohen M et al., 2003)	Yes	No	4	1072/833/833	Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders
(Tohen M et al., 2000)	Yes	No	4	NR/115/115	Medically significant disorders, Alcohol or substance abuse or dependency, Suicidal or violent
(Tohen M et al., 1999)	Yes	No	3	NR/139/139	Medically significant disorders, Alcohol or substance abuse or dependency, Suicidal or violent
(Tohen M et al., 2003)	Yes	No	2	NR/361/361	NR
(Tollefson GD et al., 1999)	Yes	No	3	115/106/106	Alcohol or substance abuse or dependency, Suicidal or violent, Previous exposure to study drug, Medically significant disorders
(van Reekum R et al., 2002)	Yes	No	5	NR/34/34	Schizophrenia, Delirium, Resistant to antipsychotic treatment, Antipsychotic use for nausea, BEHAVE-AD ≥ 3 at screening, 1 week before study, or within 2 weeks pretrial period
(Calabrese J et al., 2004)	Yes	No	2	832/542/542	DSM-IV Axis I disorder, not including primary condition studied
(Mintzer J et al., 2004)	Yes	No	2	NR/473/473	Medically significant disorders, Abnormal laboratory results, Epilepsy, Neurological or medical conditions diminishing cognitive function or that cause psychosis, Cancer, except for non-melanoma of the skin, Recent depot neuroleptic injections, Change in medications in preceding 30 dys
(Gharabawi GM et al., 2004)	Yes	No	4	489/241/241	Pregnant, lactating, psychiatric history, DSM-IV diagnosis confounded by various things, including being medically unstable, testing positive on urine drug screen, impaired hepatic or renal function, history failure of citalopram or any antidepressant with risperidone augmentation, etc.
(Daniels DG et al., 1999)	Yes	No	3	440/302/302	Resistant to antipsychotic treatment, Hospitalized > 4 weeks, Alcohol or substance abuse or dependency, Mental retardation, Organic mental disorder, Brief reactive psychosis, Depot neuroleptic within 4 weeks, Suicidal or violent
(Keck P Jr et al., 1998)	Yes	No	2	203/139/139	Nursing home/residential center resident, Resistant to antipsychotic treatment, Alcohol or substance abuse or dependency, Residual schizophrenia, Mental retardation, Organic mental disorder, Brief reactive psychosis, Suicidal or violent

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/ Enrolled	Exclusion criteria
(Bartzokis et al., 2004)	Yes	No	3	73/65/65	Alcohol or substance abuse or dependency, Suicidal or violent, Medically significant disorders, Neurological or medical conditions diminishing cognitive function, Antipsychotic medications, Seizure disorder or epilepsy or risk, Change in antidepressant regimen within 6 wk prior to study entry
(Padala PR et al., 2005)	Yes	No	2	NR/20/20	Bipolar disorder, Schizophrenia, Medically significant disorders, Abnormal laboratory results, Suicidal or violent, Pregnancy, Nursing, Previous exposure to study drug, Psychotropic use, Alcohol or substance abuse or dependency, Antipsychotics other than the ones studied
(Reich DB et al., 2004)	Yes	No	2	NR/21/21	Medically significant disorders, Alcohol or substance abuse or dependency, Psychotic disorder, Organic mental disorder, Antipsychotics other than the ones studied, Mood stabilizers, Risperidone treatment of 1 week or more, Suicidal or violent, Entry into individual psychotherapy within 3 mos of study, Entry into group therapy within 1 mo of study,
(Bystritsky A et al., 2004)	Yes	No	3	NR/26/26	DSM-IV Axis I disorder, not including primary condition studied, DSM-IV Axis II disorder, not including primary condition studied, Neurological conditions, excluding Alzheimers or vascular dementia, contributing to psychosis or dementia, Pregnant, Medically significant disorders, HAM-D > 20, Bizarre psychosis
(Buchsbaum MS, 2003)	No	No	1	NR/16/16	NR
(Erzegovesi S et al., 2005)	No	No	4	NR/45/45	Antiobsessional medications, Psychiatric disorders except for panic disorder and tic disorders, Pregnant, Contraindication to risperidone, Lactating, Seizure disorder or epilepsy or risk, Medical conditions contraindicating use of fluvoxamine
(Hollander E et al., 2003)	Yes	No	4	NR/16/16	Medically significant disorders, Schizophrenia and schizoafective disorder, Bipolar disorder
(Butterfield MI et al., 2001)	Yes	No	3	NR/15/15	Bipolar disorder, Psychotic disorder, Mental retardation, Alcohol or substance abuse or dependency, Suicidal or violent
(Stein MB et al., 2002)	Yes	No	3	NR/21/19	NR
(Hamner MB et al., 2003)	Yes	No	4	NR/40/40	Risperidone hypersensitivity,-Medically significant disorders, Alcohol or substance abuse or dependency, Schizophrenia, Bipolar disorder, Suicidal or violent
(Monnelly EP et al., 2003)	Yes	No	4	NR/16/16	Schizophrenia, Bipolar disorder with psychotic features, Organic mental disorder, Antipsychotic medications, Alcohol/substance dependency in remission
(Bogenschutz MP et al., 2004)	Yes	No	3	NR/40/40	Psychotropic medications, Pregnant, Bipolar disorder, Psychotic disorder, Major depressive disorder, Alcohol or substance abuse or dependency, Suicidal or violent, Neurological disorder

Author, Year	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/ Enrolled	Exclusion criteria
(Zanarini MC et al., 2001)	Yes	No	5	30/28/28	Previous exposure to study drug, Medically significant disorders, Seizure disorder or epilepsy or risk, Psychotropic medications, Alcohol or substance abuse or dependency, Suicidal or violent, Pregnant, Lactating
(Koenigsberg HW et al., 2003)	Yes	No	4	NR/25/25	Alcohol or substance abuse or dependency, Use psychotropic medications within 2 wks
(Sallee FR et al., 2000)	Yes	No	3	29/28/28	Abnormal laboratory results, Neuroleptic malignant syndrome, Atypical antipsychotics sensitivity, Major depressive disorder, Pervasive developmental disorder, Autism, Mental retardation, Eating disorders
(Breder C et al., 2004)	Yes	No	1	NR/487/487	NR
(De Deyn P et al., 2005)	Yes	No	3	NR/208/208	Bipolar disorder, Schizophrenia, Delirium, Amnestic disorder, Schizoaffective disorder, Mood disorders with psychotic features, Psychotic features accounted better by disease other than the one studied or by effects of a substance, Refractory to neuroleptics
(Streim JE et al., 2004)	Yes	No	2	NR/256/256	NR
(McQuade R et al., 2004)	Yes	No	2	567/161/161	NR
(Kennedy J et al., 2005)	Yes	No	3	446/268/268	DSM-IV Axis I disorder, not including primary condition studied, Neurologic disorder, not including primary conditioned studied, NPI > 1 on delusions, hallucinations, agitation/aggression or dysphoria items, Score ≥ 1 on cholinesterase inhibitor use, antioxidant or herbal supplement items ≤ 4 week
(Soler J et al., 2005)	Yes	No	2	125/60/60	DSM-IV Axis I disorder, not including primary condition studied, Psychotherapy, Sexually active females of child bearing age not using an effective contraceptive method
(Scahill L et al., 2003)	Yes	No	3	49/34/34	Major depressive disorder, Psychosis/psychotic features, Anxiety disorder, Wechsler Intelligence Scale age approximate IQ < 70, Previous adequate trial of risperidone, Medically significant disorders, Y-BOCS or CY-BOCS > 15, Psychotropic medications

Author, Year	Run-in/ Randomization Method Washout/ Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(McCracken JT et al., 2002)	2-4 week washout period for all psychotropics	NR	No - Placebo	Source: Government, Industry & Private Role: described	Yes
(Shea S et al., 2004)	NR NR	NR	No - Anticonvulsant, anti-EPS, anxiety, sleep medications only	Source: Industry Role: Described	Yes
(De Deyn PP et al., 2004)	Run-in period reported NR	NR	No - Antidepressants, benzodiazepines, acetylcholinesterase inhibitors	Source: Industry Role: NR	Yes
(Street JS et al., 2000)	Run-in period reported NR	NR	No - Benzodiazepines prn only	Source: Government, Industry & Private Role: described	Yes
(Ruths S et al., 2004)	Run-in period reported NR	No	No	Source: NR Role: NR	Yes
(Zhong X et al., 2004)	NR NR	NR	No - Placebo	Source: NR Role: NR	Yes
(Ballard CG et al., 2004)	NR NR	NR	No - Placebo	Source: Unclear Role: NR	Yes
(Brodaty H et al., 2003)	NR Washout period reported	No	No - Anti-EPS, oxazepam, sedatives prn only	Source: Industry Role: described	Yes
(Katz IR et al., 1999)	NR Washout period reported	NR	No - Anti-EPS, benzodiazepines, chloral hydrate prn only	Source: Industry Role: described	Yes
(Meguro K et al., 2004)	NR NR	NR	No	Source: Private Role: NR	Yes
(Mertens C, 1993)	Run-in period reported NR	No	No - Placebo	Source: Industry Role: NR	Yes
(Corya S et al., 2002)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(Howanitz E et al., 2001)	NR NR	NR	No - Placebo	Source: NR Role: NR	Yes
(Kinrys G et al., 2002)	Run-in period reported NR	NR	Yes	Source: Industry Role: NR	Yes
(Rothschild AJ et al., 2004)	NR NR	NR	No - Benzodiazepines prn only	Source: Industry Role: NR	Yes
(Shi L et al., 2004)	NR Washout period reported	NR	No - Anti-EPS, benzodiazepines only	Source: Industry Role: NR	Yes
(Street JS et al., 2000)	NR NR	NR	NR	Source: Industry Role: NR	Yes
(Tohen M et al., 2003)	NR Washout period reported	NR	No - Anti-EPS, benzodiazepines only	Source: Industry Role: described	Yes
(Tohen M et al., 2000)	NR Washout period reported	No	No - Lorazepam, benztropine	Source: Industry Role: NR	Yes

Author, Year	Run-in/ Randomization Method Washout/ Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Tohen M et al., 1999)	NR Washout period reported	NR	No - Lorazepam, benztropine	Source: Industry Role: NR	Yes
(Tohen M et al., 2003)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(Tollefson GD et al., 1999)	NR NR	No	No - Anti-EPS, benzodiazepines prn	Source: Industry Role: NR	Yes
(van Reekum R et al., 2002)	Run-in period reported NR	No	NR	Source: Private (Non-Industry) Role: NR	Yes
(Calabrese J et al., 2004)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(Mintzer J et al., 2004)	NR Washout period reported	No	No - Placebo	Source: Industry Role: NR	Yes
(Gharabawi GM et al., 2004)	Run-in period reported NR	No	Yes	Source: Industry Role: NR	Yes
(Daniels DG et al., 1999)	NR Washout period reported	No	No - Lorazepam, benztropine, beta-blockers only	Source: Industry Role: NR	Yes
(Keck P Jr et al., 1998)	NR Washout period reported	NR	No - Lorazepam, benztropine, beta-blockers only	Source: Industry Role: NR	Yes
(Bartzokis G et al., 2004)	NR NR	NR	Yes	Source: Government, Industry & Private Role: NR	Yes
(Padala PR et al., 2005)	NR Washout period reported	NR	No - Placebo	Source: Industry Role: NR	Yes
(Reich DB et al., 2004)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Bystritsky A et al., 2004)	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Buchsbaum MS, 2003)	NR NR	NR	NR	Source: NR Role: NR	Limited
(Erzegovesi S et al., 2005)	Run-in period reported NR	NR	Yes	Source: NR Role: NR	Yes
(Hollander E et al., 2003)	NR NR	NR	Yes	Source: Industry & Private Role: described	Yes
(Butterfield MI et al., 2001)	NR NR	NR	NR	Source: Industry Role: NR	Yes
(Stein MB et al., 2002)	Run-in period reported NR	NR	No - SRI	Source: Industry Role: NR	Yes
(Hamner MB et al., 2003)	Run-in period reported Washout period reported	No	Yes	Source: Industry Role: described	Yes

Author, Year	Run-in/ Randomization Method Washout/ Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Monnelly EP et al., 2003)	NR NR	Yes	Yes	Source: Government & Industry Role: NR	Yes
(Bogenschutz MP et al., 2004)	NR NR	No	Yes	Source: Industry Role: NR	Yes
(Zanarini MC et al., 2001)	NR NR	No	NR	Source: Industry Role: NR	Limited
(Koenigsberg HW et al., 2003)	Run-in period reported NR	NR	No - No other psychotropic medications allowed	Source: Government & Industry Role: described	Yes
(Sallee FR et al., 2000)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(Breder C et al., 2004)	NR Washout period reported	NR	No - Placebo	Source: Industry Role: NR	Yes
(De Deyn P et al., 2005)	NR Washout period reported	No	No - Placebo	Source: Industry Role: NR	Yes
(Streim JE et al., 2004)	NR NR	NR	No - Placebo	Source: Industry Role: NR	Yes
(McQuade R et al., 2004)	Run-in period reported NR	No	No - Placebo	Source: Industry Role: NR	Yes
(Kennedy J et al., 2005)	NR Washout period reported	No	Yes	Source: Industry Role: NR	Yes
(Soler J et al., 2005)	NR NR	NR	Yes	Source: Government & Industry Role: NR	Yes
(Scahill L et al., 2003)	NR Washout period reported	No	No - Placebo	Source: Government, Industry & Private Role: NR	Yes

Acronyms in Evidence Table:

CCT	Clinical control trial
kg	kilograms
lbs	pounds
ND	Not described
NOS	Not otherwise specified
NR	Not reported
RCT	Randomized control trial
RR	Risk ratio
SMD	Standard mean difference
WMD	Weighted mean difference

Outcomes:

ABC	Aberrant Behavior Checklist
ACES	Agitation-Calmness Evaluation Scale
ADAS-cog	Alzheimer's Disease Assessment Scale
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AIAQ	Anger, Irritability, and Assault Questionnaire
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HAM-D/HDRS	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment

MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale
NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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C8: Quality Tables – Augmentation Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
(Tohen M et al., 2002)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described
(Yargic LI et al., 2004)	Method NR	Method NR	Yes	Yes	Yes	No	No
(Atmaca M et al., 2002)	Method NR	Method NR	Yes	Yes	NR	NR	NR
(Denys D et al., 2004)	Method NR	Method NR	Yes	Yes	Yes	Yes	Yes
(Cavedini P et al., 2004)	Yes	Method NR	Yes	Yes	Yes	No	Yes
(McDougle CJ et al., 2000)	Yes	Method NR	Yes	Yes	Yes	Yes, but not described	Yes, but not described
(Shapira NA et al., 2004)	Method NR	Method NR	Yes	Yes	NR	Yes, but not described	Yes, but not described
(Dunner D et al., 2003)	Method NR	Method NR	Yes	Yes	Yes	No	No
(Carey PD et al., 2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(Fineberg NA et al., 2005)	Method NR	Method NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes, but not described
(Li X et al., 2005)	Method NR	Method NR	NR	Yes	NR	Yes, but not described	Yes, but not described

Author, Year	Attrition, crossovers, adherence, contamination	Loss to follow-up: differential/high	Intention-to-treat analysis	Post-randomization exclusions	Quality rating (Jadad score)	Number screened/ Eligible/Enrolled
(Tohen M et al., 2002)	Yes/NR /NR /NR	No	Yes	No	3	501/344/344
(Yargic LI et al., 2004)	Yes/NR /NR /NR	NR	No	No	2	NR/120/NR
(Atmaca M et al., 2002)	Yes/NR /NR /NR	No	Yes	No	2	52/27/27
(Denys D et al., 2004)	Yes/NR /NR /NR	No	Yes	No	4	NR/40/40
(Cavedini P et al., 2004)	NR /NR /NR /NR	NR	No	No	4	NR/30/30
(McDougle CJ et al., 2000)	Yes/NR /NR /NR	No	Yes	No	4	70/36/36
(Shapira NA et al., 2004)	Yes/NR /NR /NR	No	Yes	No	3	74/44/44
(Dunner D et al., 2003)	NR /NR /Yes/NR	NR	Yes	No	1	90/64/64
(Carey PD et al., 2005)	Yes/NR /NR /NR	No	Yes	Yes, exclusions reported by group:0/1/.	5	NR/42/42
(Fineberg NA et al., 2005)	Yes/NR /NR /NR	No	Yes	No	3	NR/21/21
(Li X et al., 2005)	Yes/Yes/Yes/NR	NR	No	No	2	27/16/16

Author, Year	Exclusion criteria	Run-in/Randomization Method Washout/Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Tohen M et al., 2002)	NR	NR Washout period reported	NR	Yes	Source: Industry Role: NR	Yes
(Yargic LI et al., 2004)	HAM-D Item 3 > 2, Psychotic disorder, Use psychotropic medications within 4 wks, Medically significant disorders, Abnormal laboratory results, Bipolar disorder, Alcohol or substance abuse or dependency, Pregnant	NR NR	NR	Yes	Source: NR Role: NR	Yes
(Atmaca M et al., 2002)	NR	Run-in period reported NR	NR	Yes	Source: NR Role: NR	Yes
(Denys D et al., 2004)	Tic disorder, Tourettes disorder, Major depressive disorder, Pregnant, Organic mental disorder, Seizure disorder or epilepsy or risk, Neurological disorder, Bipolar disorder	NR NR	NR	Yes	Source: Industry Role: NR	Yes
(Cavedini P et al., 2004)	DSM-IV Axis I disorder, not including primary condition studied, Tic disorder, Medically significant disorders, Severe internal or neurological disease, Brain injury or head trauma, Alcohol or substance abuse or dependency	NR NR	Yes	Yes	Source: NR Role: NR	Yes
(McDougle CJ et al., 2000)	Non-healthy, Pregnant, Use psychotropic medications within 4 wks	Run-in period reported NR	NR	Yes	Source: Government & Private Role: described	Yes
(Shapira NA et al., 2004)	Major depressive disorder, Psychotic disorder, Bipolar disorder, Alcohol or substance abuse or dependency, Seizure disorder or epilepsy or risk, Encephalitis, Brain injury or head trauma, Medically significant disorders	Run-in period reported NR	NR	Yes	Source: Government & Industry Role: NR	Yes
(Dunner D et al., 2003)	NR	Run-in period reported NR	NR	Yes	Source: Industry Role: NR	Yes

Author, Year	Exclusion criteria	Run-in/Randomization Method Washout/Randomization Method	Class naïve patients only	Control group standard of care	Funding	Relevance
(Carey PD et al., 2005)	Lactating, Sexually active females of child bearing age not using an effective contraceptive method, Medically significant disorders, Brain injury or head trauma, Co-existing Axis -I disorder unless deemed to be secondary to OCD, Brain Surgery, Seizure disorder or epilepsy or risk, Medications that that interact with Quetiapine	Run-in period reported NR	No	Yes	Source: Industry Role: NR	Yes
(Fineberg NA et al., 2005)	DSM-IV Axis I disorder, not including primary condition studied, DSM-IV Axis I disorder, not including primary condition studied or depression with MADRS < 30, Tourettes disorder, Resistant to antipsychotic treatment	NR NR	No	Yes	Source: Industry Role: described	Yes
(Li X et al., 2005)	DSM-IV Axis I disorder, not including primary condition studied, SADS-L (Schedule for Affective Disorders and Schizophrenia - Lifetime version) Criteria, Major motor disorder, Vocal tics	Run-in period reported Washout period reported	NR	Yes	Source: Industry Role: NR	Yes

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MMSE	Mini-Mental State Examination
M-NCAS	Modified Strain in Nursing Care Assessment
MOSES	Multidimentional Observational Scale for Elderly Subjects
MOVES	Motor Tic, Obsessions, and Compulsions, Vocal Tic Evaluation Survey
N-CBRF	Nisonger Child Behavior Rating Scale
NIMH-OC	National Institute of Mental Health Obsessive-Compulsive Scale

NPI	Neuropsychiatric Inventory
NPI/NH	Neuropsychiatric Inventory/Nursing Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OAS-M	Overt Aggression Scale-Modified
PANSS	Positive and Negative Symptom Scale
PCL-M	Patient Checklist for PTSD--Military Version
PDC	Depression cluster
PDS	Progressive Deterioration Scale
PGDRS	Psychogeriatric Dependency Rating Scale
PGI	Patient Global Impressions
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLS	Quality of Life Scales
QUALID	Quality of Life in Late-Stage Dementia Scale
ROAS	Retrospective Overt Aggression Scale
SANS	Scale for the Assessment of Negative Symptoms
SCL-90	Symptom Checklist-90
SDS	Sheehan Disability Scale
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIB	Severe Impairment Battery
SIB-Q	Self-injurious Behavior Questionnaire
SIP	Structured Interview for PTSD
SPQ	Schizotypal Personality Questionnaire
SPRINT	Short PTSD Rating Interview
STAS-AX	State-Trait Anger Expression Inventory
STAT-S	Spielberger State-Trait Anger Scale, state version
STAT-T	Spielberger State-Trait Anger Scale, trait version
TOP-8	Treatment Outcome PTSD Scale
TSSS	Tourette's Syndrome Severity Scale
VAS	Visual Analog Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

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Table A. Dementia studies – Atypical Antipsychotics Compared to Placebo

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI	NNH[1]	95% CI NNH
			# adverse events	sample size	# adverse events	sample size				
Anticholinergic Events	Olanzapine	1	12	90	60	178	3.29	(1.62, 7.17)	5.00	(3.00, 10.00)
Appetite or Weight/Decrease	Aripiprazol	1	13	121	23	122	1.93	(0.88, 4.38)	NC	NC
Appetite or Weight/Decrease	Olanzapine	2	15	141	32	363	0.75	(0.38, 1.56)	NC	NC
Appetite or Weight/Decrease	Risperidone	1	8	94	11	196	0.64	(0.23, 1.90)	NC	NC
Appetite or Weight/Increase	Aripiprazol	1	3	102	5	106	1.63	(0.31, 10.78)	NC	NC
Appetite or Weight/Increase	Olanzapine	2	2	184	24	382	6.12	(1.49, 54.04)	19.00	(12.00, 43.00)
Appetite or Weight/Increase	Risperidone	1	1	94	6	196	2.93	(0.35, 136.52)	NC	NC
Cardiovascular	Aripiprazol	1	10	121	32	122	4.22	(1.84, 10.63)	6.00	(4.00, 11.00)
Cardiovascular	Olanzapine	4	5	298	38	678	3.31	(1.27, 10.91)	25.00	(16.00, 60.00)
Cardiovascular	Risperidone	4	27	665	110	1060	2.33	(1.48, 3.78)	16.00	(12.00, 25.00)
Cardiovascular/BP/Decrease	Aripiprazol	1	6	125	4	131	0.63	(0.13, 2.71)	NC	NC
Cardiovascular/BP/Increase	Aripiprazol	1	5	102	4	106	0.76	(0.15, 3.65)	NC	NC
Cardiovascular/BP/Increase	Olanzapine	1	1	67	2	137	0.98	(0.05, 58.55)	NC	NC
Cardiovascular/Rhythm	Aripiprazol	1	1	102	2	106	1.94	(0.10, 115.71)	NC	NC
Cardiovascular/Rhythm	Olanzapine	1	2	67	3	137	0.73	(0.08, 8.92)	NC	NC
Cardiovascular/Rhythm	Risperidone	1	6	19	7	20	1.16	(0.25, 5.49)	NC	NC
Constitutional/Fever or Infection	Olanzapine	3	5	231	38	541	3.23	(1.23, 10.71)	21.00	(13.00, 50.00)
Constitutional/Fever or Infection	Risperidone	3	19	427	59	825	1.41	(0.80, 2.57)	NC	NC
Dermatologic	Aripiprazol	2	52	246	96	253	2.35	(1.54, 3.62)	6.00	(4.00, 11.00)
Dermatologic	Olanzapine	1	7	47	19	159	0.78	(0.29, 2.35)	NC	NC
Dermatologic	Risperidone	2	82	333	133	629	1.24	(0.87, 1.79)	NC	NC
Endocrine/Diabetes	Risperidone	1	5	238	4	235	0.81	(0.16, 3.80)	NC	NC
Endocrine/Prolactin	Risperidone	1	0	238	0	235	NC	NC	NC	NC
Gastrointestinal	Aripiprazol	2	18	246	45	253	2.72	(1.48, 5.18)	10.00	(6.00, 21.00)
Gastrointestinal	Olanzapine	1	6	90	24	178	2.18	(0.82, 6.77)	NC	NC
Gastrointestinal	Risperidone	1	61	170	38	167	0.53	(0.32, 0.87)	-8.00	(-28.00, -4.00)
HEENT	Olanzapine	1	3	47	16	159	1.64	(0.44, 9.17)	NC	NC
HEENT	Risperidone	2	27	333	80	629	1.27	(0.78, 2.12)	NC	NC
HEENT/Eye	Risperidone	1	18	170	20	167	1.15	(0.55, 2.40)	NC	NC
Heme	Risperidone	1	12	238	8	235	0.66	(0.23, 1.81)	NC	NC

NC = Not Calculated

Table A. Dementia studies – Atypical Antipsychotics Compared to Placebo - continued

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI	NNH[1]	95% CI NNH
			# adverse events	sample size	# adverse events	sample size				
Infections	Olanzapine	1	5	90	10	178	1.01	(0.30, 3.90)	NC	NC
Infections	Risperidone	2	33	333	54	629	1.05	(0.64, 1.75)	NC	NC
Liver Function Test Abnormality	Aripiprazol	1	1	102	0	106	0.00	(0.00, 37.53)	NC	NC
Musculoskeletal	Olanzapine	1	3	90	0	178	0.00	(0.00, 1.21)	NC	NC
Neuro	Olanzapine	3	35	326	95	482	2.23	(1.43, 3.55)	11.00	(7.00, 24.00)
Neuro	Quetiapine	1	16	142	13	94	1.26	(0.53, 2.97)	NC	NC
Neuro	Risperidone	2	26	236	44	281	1.50	(0.85, 2.70)	NC	NC
Neuro/CVA	Aripiprazol	1	1	102	1	106	0.96	(0.01, 76.25)	NC	NC
Neuro/CVA	Olanzapine	2	2	232	5	278	2.09	(0.32, 23.27)	NC	NC
Neuro/CVA	Quetiapine	1	1	142	1	94	1.51	(0.02, 119.85)	NC	NC
Neuro/CVA	Risperidone	3	6	550	21	487	3.88	(1.49, 11.91)	31.00	(19.00, 82.00)
Neuro/Fatigue	Aripiprazol	2	14	246	41	253	3.67	(1.83, 7.90)	10.00	(6.00, 19.00)
Neuro/Fatigue	Olanzapine	3	9	326	36	482	2.37	(1.08, 5.75)	21.00	(13.00, 57.00)
Neuro/Fatigue	Quetiapine	1	2	142	4	94	3.10	(0.43, 34.89)	NC	NC
Neuro/Fatigue	Risperidone	2	4	236	20	281	3.56	(1.13, 14.96)	18.00	(11.00, 50.00)
Neuro/Headache	Olanzapine	2	2	209	9	237	4.86	(0.95, 48.01)	NC	NC
Neuro/Headache	Quetiapine	1	2	142	1	94	0.75	(0.01, 14.67)	NC	NC
Neuro/Headache	Risperidone	2	13	312	13	252	1.17	(0.49, 2.81)	NC	NC
Neuro/Movement Disorder/EPS	Aripiprazol	3	16	348	39	359	2.53	(1.34, 5.01)	16.00	(10.00, 42.00)
Neuro/Movement Disorder/EPS	Olanzapine	1	1	142	12	100	19.04	(2.73, 827.61)	9.00	(6.00, 21.00)
Neuro/Movement Disorder/EPS	Quetiapine	1	1	142	2	94	3.05	(0.16, 182.09)	NC	NC
Neuro/Movement Disorder/EPS	Risperidone	4	29	713	114	949	2.82	(1.81, 4.51)	13.00	(10.00, 18.00)
Neuro/Movement Disorder/Gait	Olanzapine	4	15	373	79	641	2.75	(1.52, 5.29)	12.00	(9.00, 20.00)
Neuro/Movement Disorder/Gait	Quetiapine	1	3	142	3	94	1.52	(0.20, 11.63)	NC	NC
Neuro/Movement Disorder/Gait	Risperidone	3	8	406	32	448	3.04	(1.32, 7.84)	19.00	(13.00, 41.00)
Neuro/Movement Disorder/Tardive Dyskinesia	Olanzapine	1	4	142	3	100	1.07	(0.15, 6.46)	NC	NC
Neuro/Movement Disorder/Tardive Dyskinesia	Quetiapine	1	4	142	2	94	0.75	(0.07, 5.36)	NC	NC
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	3	14	475	4	714	0.31	(0.07, 1.03)	NC	NC
Neuro/Pain	Aripiprazol	1	7	121	32	122	5.52	(2.25, 15.57)	5.00	(3.00, 9.00)
Neuro/Pain	Olanzapine	2	10	137	36	337	1.31	(0.60, 3.10)	NC	NC

NC = Not Calculated

Table A. Dementia studies – Atypical Antipsychotics Compared to Placebo - continued

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH[1]	95% CI NNH
Neuro/Pain	Risperidone	1	13	163	33	462	0.89	(0.44, 1.89)	NC	NC
Neuro/Sedation	Aripiprazol	3	10	348	54	359	6.68	(3.19, 15.72)	8.00	(6.00, 12.00)
Neuro/Sedation	Olanzapine	5	24	440	152	778	4.26	(2.66, 7.08)	7.00	(6.00, 9.00)
Neuro/Sedation	Quetiapine	1	7	142	21	94	5.51	(2.13, 16.08)	6.00	(4.00, 12.00)
Neuro/Sedation	Risperidone	6	87	922	249	1260	2.50	(1.89, 3.34)	10.00	(8.00, 13.00)
Psychiatric/Aggression	Olanzapine	1	1	94	14	204	6.82	(1.01, 292.81)	17.00	(10.00, 57.00)
Psychiatric/Aggression	Risperidone	2	19	264	22	363	0.91	(0.45, 1.85)	NC	NC
Psychiatric/Agitation	Aripiprazol	1	19	121	37	122	2.24	(1.16, 4.47)	7.00	(4.00, 24.00)
Psychiatric/Agitation	Olanzapine	4	36	373	76	641	1.19	(0.76, 1.90)	NC	NC
Psychiatric/Agitation	Quetiapine	1	14	142	11	94	1.21	(0.47, 3.03)	NC	NC
Psychiatric/Agitation	Risperidone	5	102	807	120	1145	0.84	(0.62, 1.14)	NC	NC
Psychiatric/Anxiety	Olanzapine	4	19	373	40	641	1.04	(0.57, 1.95)	NC	NC
Psychiatric/Anxiety	Quetiapine	1	3	142	0	94	0.00	(0.00, 3.65)	NC	NC
Psychiatric/Anxiety	Risperidone	2	12	236	20	281	0.89	(0.39, 2.12)	NC	NC
Psychiatric/Cognitive	Olanzapine	2	3	232	15	278	4.00	(1.08, 22.38)	24.00	(14.00, 93.00)
Psychiatric/Cognitive	Quetiapine	1	1	142	0	94	0.00	(0.00, 58.92)	NC	NC
Psychiatric/Cognitive	Risperidone	1	1	142	1	85	1.67	(0.02, 132.68)	NC	NC
Psychiatric/Depression	Olanzapine	2	4	232	16	278	3.05	(0.94, 13.04)	NC	NC
Psychiatric/Depression	Quetiapine	1	2	142	2	94	1.52	(0.11, 21.30)	NC	NC
Psychiatric/Depression	Risperidone	1	2	142	0	85	0.00	(0.00, 8.90)	NC	NC
Psychiatric/Psychotic	Olanzapine	3	14	326	62	482	2.81	(1.49, 5.64)	12.00	(8.00, 21.00)
Psychiatric/Psychotic	Quetiapine	1	3	142	0	94	0.00	(0.00, 3.65)	NC	NC
Psychiatric/Psychotic	Risperidone	2	13	236	32	281	1.35	(0.65, 2.96)	NC	NC
Psychiatric/Sleep	Olanzapine	3	13	326	30	482	1.50	(0.73, 3.26)	NC	NC
Psychiatric/Sleep	Quetiapine	1	5	142	5	94	1.54	(0.34, 6.88)	NC	NC
Psychiatric/Sleep	Risperidone	3	24	474	28	516	1.03	(0.56, 1.92)	NC	NC
Pulmonary	Aripiprazol	1	3	102	6	106	1.97	(0.41, 12.54)	NC	NC
Pulmonary	Olanzapine	1	3	94	0	204	0.00	(0.00, 1.10)	NC	NC
Pulmonary	Risperidone	1	3	94	6	196	0.96	(0.20, 6.05)	NC	NC
Severe	Risperidone	2	36	333	97	629	1.49	(0.96, 2.33)	NC	NC

NC = Not Calculated

Table A. Dementia studies – Atypical Antipsychotics Compared to Placebo - continued

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI	NNH[1]	95% CI NNH
			# adverse events	sample size	# adverse events	sample size				
Trauma	Aripiprazol	3	61	348	126	359	3.12	(2.09, 4.72)	6.00	(4.00, 9.00)
Trauma	Olanzapine	5	50	440	114	778	1.31	(0.89, 1.96)	NC	NC
Trauma	Quetiapine	1	21	142	7	94	0.46	(0.16, 1.20)	NC	NC
Trauma	Risperidone	5	289	807	403	1145	0.79	(0.63, 0.99)	-163.0	(27.00, -20.00)
Urinary	Aripiprazol	3	45	348	115	359	4.07	(2.61, 6.44)	5.00	(4.00, 8.00)
Urinary	Olanzapine	1	1	94	19	204	9.51	(1.47, 401.07)	12.00	(8.00, 27.00)
Urinary	Risperidone	4	71	665	164	1060	1.55	(1.13, 2.13)	21.00	(13.00, 63.00)

NC = Not Calculated

Table B. Dementia studies – Atypical Antipsychotics Compared to Acetylcholinesterase inhibitors

Adverse Events	Drug	# of studies	Acetylcholinesterase inhibitors		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Risperidone	1	0	14	0	13	NC	NC
Gastrointestinal	Risperidone	1	10	14	2	13	0.10	(0.01, 0.78)
Neuro/Fatigue	Risperidone	1	2	14	1	13	1.09	(0.01, 92.68)
Neuro/Movement Disorder/EPS	Risperidone	1	0	14	2	13	+Inf	(0.03, Inf+)
Neuro/Sedation	Risperidone	1	0	14	4	13	+Inf	(0.88, Inf+)
Psychiatric/Agitation	Risperidone	1	1	14	1	13	+Inf	(0.03, Inf+)

NC = Not Calculated

Table C. Dementia studies – Atypical Antipsychotics Compared to Benzodiazepines

Adverse Events	Drug	# of studies	Benzodiazepines		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Cardiovascular	Olanzapine	1	0	68	2	137	+Inf	(0.09, Inf+)
Cardiovascular/BP/Increase	Olanzapine	1	2	68	2	137	0.49	(0.03, 6.91)
Cardiovascular/Rhythm	Olanzapine	1	0	68	3	137	+Inf	(0.20, Inf+)
Neuro/Headache	Olanzapine	1	1	68	4	137	2.01	(0.19, 100.69)
Neuro/Sedation	Olanzapine	1	7	68	5	137	0.33	(0.08, 1.27)
Trauma	Olanzapine	1	3	68	3	137	0.49	(0.06, 3.74)

NC = Not Calculated

Table D. Dementia studies – Atypical Antipsychotics Compared to Conventional Antipsychotics

Adverse Events	Drug	# of studies	Conventionals		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Increase	Olanzapine	1	0	20	6	20	+Inf	(1.48, Inf+)
Appetite or Weight/Increase	Risperidone	1	0	20	0	20	NC	NC
Cardiovascular/BP/Decrease	Olanzapine	1	7	20	2	20	0.11	(0.00, 1.01)
Cardiovascular/BP/Decrease	Risperidone	1	7	20	4	20	0.47	(0.08, 2.36)
Cardiovascular/Rhythm	Olanzapine	1	5	20	0	20	0.00	(0.00, 0.98)
Cardiovascular/Rhythm	Risperidone	1	5	20	2	20	0.17	(0.00, 1.80)
Endocrine/Diabetes	Olanzapine	1	0	20	1	20	+Inf	(0.03, Inf+)
Endocrine/Diabetes	Risperidone	1	0	20	0	20	NC	NC
Gastrointestinal	Olanzapine	1	8	20	3	20	0.29	(0.04, 1.55)
Gastrointestinal	Risperidone	2	10	49	6	49	0.43	(0.10, 1.65)
HEENT/Decreased Salivation	Olanzapine	1	6	20	0	20	0.00	(0.00, 0.72)
HEENT/Decreased Salivation	Risperidone	1	6	20	0	20	0.00	(0.00, 0.72)
Neuro	Olanzapine	1	3	20	3	20	1.06	(0.12, 9.13)
Neuro	Risperidone	1	3	20	0	20	0.00	(0.00, 2.34)
Neuro/CVA	Olanzapine	2	116	5478	97	5347	1.11	(0.83, 1.49)
Neuro/CVA	Quetiapine	2	116	5478	44	2057	1.11	(0.76, 1.59)
Neuro/CVA	Risperidone	2	116	5478	229	9676	1.35	(1.07, 1.71)
Neuro/Fatigue	Olanzapine	1	0	20	0	20	NC	NC
Neuro/Fatigue	Risperidone	1	0	20	2	20	+Inf	(0.03, Inf+)
Neuro/Movement Disorder/Akathisia	Olanzapine	1	0	20	1	20	NC	NC
Neuro/Movement Disorder/Akathisia	Risperidone	1	0	20	0	20	NC	NC
Neuro/Movement Disorder/EPS	Olanzapine	1	4	20	0	20	0.00	(0.00, 1.42)
Neuro/Movement Disorder/EPS	Risperidone	1	4	20	2	20	0.23	(0.00, 2.65)
Neuro/Sedation	Olanzapine	1	2	20	6	20	4.01	(0.59, 46.77)
Neuro/Sedation	Risperidone	3	25	163	18	164	0.68	(0.33, 1.36)
Psychiatric/Sexual	Olanzapine	1	0	20	0	20	NC	NC
Psychiatric/Sexual	Risperidone	1	0	20	1	20	NC	NC
Psychiatric/Sleep	Olanzapine	1	0	20	0	20	NC	NC
Psychiatric/Sleep	Risperidone	1	0	20	1	20	NC	NC
Urinary	Risperidone	1	0	29	1	29	+Inf	(0.03, Inf+)

NC = Not Calculated

Table E. Dementia studies – Atypical Antipsychotic Compared to Another Atypical Antipsychotic

Adverse Events	Atypical antipsychotic 1	Atypical antipsychotic 2	# of studies	Atypical antipsychotic 1		Atypical antipsychotic 2		Pooled OR	95% CI
				# adverse events	sample size	# adverse events	sample size		
Cardiovascular/Rhythm	Risperidone	Olanzapine	1	0	19	1	20	+Inf	(0.02, Inf+)
Gastrointestinal	Risperidone	Olanzapine	1	1	20	0	20	NC	NC
Neuro	Quetiapine	Olanzapine	1	13	94	27	100	2.30	(1.34, 4.04)
Neuro	Risperidone	Olanzapine	1	13	85	27	100	2.04	(0.93, 4.67)
Neuro	Risperidone	Quetiapine	1	13	85	13	94	0.89	(0.35, 2.23)
Neuro/CVA	Quetiapine	Olanzapine	4	55	3877	105	14273	0.84	(0.66, 1.08)
Neuro/CVA	Risperidone	Olanzapine	3	60	11906	36	11854	0.71	(0.46, 1.10)
Neuro/CVA	Risperidone	Quetiapine	4	253	17445	55	3877	0.92	(0.67, 1.25)
Neuro/Fatigue	Quetiapine	Olanzapine	1	4	94	3	100	0.70	(0.20, 2.34)
Neuro/Fatigue	Risperidone	Olanzapine	1	3	85	3	100	0.85	(0.11, 6.49)
Neuro/Fatigue	Risperidone	Quetiapine	1	3	85	4	94	1.21	(0.20, 8.53)
Neuro/Headache	Quetiapine	Olanzapine	1	1	94	5	100	4.88	(1.02, 46.38)
Neuro/Headache	Risperidone	Olanzapine	1	5	85	5	100	0.84	(0.19, 3.80)
Neuro/Headache	Risperidone	Quetiapine	1	5	85	1	94	0.17	(0.00, 1.60)
Neuro/Movement Disorder/EPS	Quetiapine	Olanzapine	1	2	94	12	100	6.25	(2.09, 25.27)
Neuro/Movement Disorder/EPS	Risperidone	Olanzapine	1	10	85	12	100	1.02	(0.38, 2.81)
Neuro/Movement Disorder/EPS	Risperidone	Quetiapine	1	10	85	2	94	0.16	(0.02, 0.81)
Neuro/Movement Disorder/Gait	Quetiapine	Olanzapine	1	3	94	4	100	1.26	(0.38, 4.51)
Neuro/Movement Disorder/Gait	Risperidone	Olanzapine	1	1	85	4	100	3.48	(0.34, 174.38)
Neuro/Movement Disorder/Gait	Risperidone	Quetiapine	1	1	85	3	94	2.75	(0.22, 147.08)
Neuro/Movement Disorder/Tardive Dyskinesia	Quetiapine	Olanzapine	1	2	94	3	100	1.42	(0.33, 6.96)
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	Olanzapine	1	3	85	3	100	0.85	(0.11, 6.49)
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	Quetiapine	1	3	85	2	94	0.60	(0.05, 5.34)
Neuro/Sedation	Quetiapine	Olanzapine	1	21	94	24	100	1.10	(0.67, 1.81)
Neuro/Sedation	Risperidone	Olanzapine	3	52	352	77	388	1.47	(0.98, 2.22)
Neuro/Sedation	Risperidone	Quetiapine	1	13	85	21	94	1.59	(0.70, 3.74)
Psychiatric/Agitation	Quetiapine	Olanzapine	1	11	94	7	100	0.57	(0.26, 1.21)
Psychiatric/Agitation	Risperidone	Olanzapine	1	5	85	7	100	1.20	(0.31, 5.00)
Psychiatric/Agitation	Risperidone	Quetiapine	1	5	85	11	94	2.11	(0.64, 8.11)
Psychiatric/Anxiety	Quetiapine	Olanzapine	1	0	94	3	100	+Inf	(1.12, Inf+)

NC = Not Calculated

Table E. Dementia studies – Atypical Antipsychotic Compared to Another Atypical Antipsychotic - continued

Adverse Events	Atypical antipsychotic 1	Atypical antipsychotic 2	# of studies	Atypical antipsychotic 1		Atypical antipsychotic 2		Pooled OR	95% CI
				# adverse events	sample size	# adverse events	sample size		
Psychiatric/Anxiety	Risperidone	Olanzapine	1	0	85	3	100	+Inf	(0.35, Inf+)
Psychiatric/Anxiety	Risperidone	Quetiapine	1	0	85	0	94	NC	NC
Psychiatric/Cognitive	Quetiapine	Olanzapine	1	0	94	5	100	+Inf	(2.17, Inf+)
Psychiatric/Cognitive	Risperidone	Olanzapine	1	1	85	5	100	4.39	(0.48, 211.54)
Psychiatric/Cognitive	Risperidone	Quetiapine	1	1	85	0	94	0.00	(0.00, 35.27)
Psychiatric/Depression	Quetiapine	Olanzapine	1	2	94	4	100	1.91	(0.50, 8.83)
Psychiatric/Depression	Risperidone	Olanzapine	1	0	85	4	100	+Inf	(0.57, Inf+)
Psychiatric/Depression	Risperidone	Quetiapine	1	0	85	2	94	+Inf	(0.17, Inf+)
Psychiatric/Psychotic	Quetiapine	Olanzapine	1	0	94	7	100	+Inf	(3.28, Inf+)
Psychiatric/Psychotic	Risperidone	Olanzapine	1	0	85	7	100	+Inf	(1.27, Inf+)
Psychiatric/Psychotic	Risperidone	Quetiapine	1	0	85	0	94	NC	NC
Psychiatric/Sleep	Quetiapine	Olanzapine	1	5	94	5	100	0.94	(0.34, 2.57)
Psychiatric/Sleep	Risperidone	Olanzapine	1	4	85	5	100	1.07	(0.22, 5.56)
Psychiatric/Sleep	Risperidone	Quetiapine	1	4	85	5	94	1.14	(0.24, 5.93)
Trauma	Quetiapine	Olanzapine	1	7	94	17	100	2.54	(1.27, 5.32)
Trauma	Risperidone	Olanzapine	1	10	85	17	100	1.53	(0.62, 3.99)
Trauma	Risperidone	Quetiapine	1	10	85	7	94	0.61	(0.19, 1.86)

NC = Not Calculated

Table F. Dementia studies – Risperidone with Rivastigamine Compared to Rivastigamine

		Rivastigamine		Risperidone + Rivastigamine			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Decrease	1	0	14	14	63	+Inf	(0.75, +Inf)
Gastrointestinal	1	10	14	30	63	0.40	(0.08, 1.60)
Neuro/Fatigue	1	2	14	17	63	4.12	(0.53, 189.40)
Neuro/Movement Disorder/EPS	1	0	14	3	63	+Inf	(0.04, +Inf)
Neuro/Sedation	1	0	14	17	63	+Inf	(1.09, +Inf)
Psychiatric/Agitation	1	1	14	7	63	+Inf	(0.30, +Inf)

NC = Not Calculated

Table G. Autism/Tourette's studies – Atypical Antipsychotics Compared to Placebo

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Accidental Overdose	Risperidone	1	1	39	1	40	0.97	(0.01, 78.47)
Appetite or Weight/Decrease	Risperidone	3	7	109	8	105	1.20	(0.37, 4.03)
Appetite or Weight/Increase	Risperidone	3	20	149	56	144	5.94	(2.94, 12.62)
Cardiovascular/BP/Decrease	Risperidone	2	1	91	11	89	12.47	(1.75, 547.58)
Cardiovascular/Rhythm	Risperidone	1	1	52	0	49	0.00	(0.00, 41.39)
Constitutional/Fever or Infection	Risperidone	2	19	131	20	128	1.10	(0.52, 2.30)
Dermatologic	Risperidone	1	7	52	11	49	1.85	(0.59, 6.22)
Endocrine	Ziprasidone	1	0	12	1	16	+Inf	(0.02, Inf+)
Endocrine/Prolactin	Ziprasidone	1	0	12	5	16	+Inf	(0.78, Inf+)
Gastrointestinal	Risperidone	3	54	109	68	105	3.24	(1.41, 7.92)
HEENT	Risperidone	2	33	91	49	89	2.31	(1.19, 4.54)
HEENT/Decreased Salivation	Risperidone	1	5	52	9	49	2.10	(0.58, 8.66)
HEENT/Eye	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)
HEENT/Increased Salivation	Risperidone	2	4	91	17	89	5.35	(1.63, 23.08)
Infections	Risperidone	2	8	91	20	89	3.12	(1.18, 9.02)
Liver Function Test Abnormality	Risperidone	1	2	52	1	49	0.52	(0.01, 10.37)
Neuro	Risperidone	2	5	70	8	65	1.81	(0.49, 7.40)
Neuro/Fatigue	Risperidone	3	16	109	39	105	4.40	(2.04, 9.94)
Neuro/Headache	Risperidone	2	8	91	14	89	1.96	(0.72, 5.72)
Neuro/Movement Disorder	Risperidone	1	0	79	3	79	+Inf	(0.42, Inf+)
Neuro/Movement Disorder/Akathisia	Ziprasidone	1	0	12	1	16	+Inf	(0.02, Inf+)
Neuro/Movement Disorder/EPS	Risperidone	2	9	131	34	128	4.85	(2.15, 12.08)
Neuro/Movement Disorder/Gait	Risperidone	1	2	39	0	40	0.00	(0.00, 5.17)
Neuro/Movement Disorder/Tardive Dyskinesia	Risperidone	2	5	91	6	89	1.27	(0.31, 5.55)
Neuro/Sedation	Risperidone	3	10	109	56	105	12.09	(5.40, 29.61)
Neuro/Sedation	Ziprasidone	1	5	12	12	16	3.97	(0.66, 28.56)
Psychiatric	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)
Psychiatric/Aggression	Risperidone	1	0	39	1	40	+Inf	(0.02, Inf+)
Psychiatric/Agitation	Risperidone	1	3	52	3	49	1.06	(0.14, 8.36)

NC = Not Calculated

Table G. Autism/Tourette's studies – Atypical Antipsychotics Compared to Placebo (continued)

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Psychiatric/Anxiety	Risperidone	1	10	52	12	49	1.36	(0.47, 3.96)
Psychiatric/Apathy	Risperidone	1	0	39	5	40	+Inf	(0.94, Inf+)
Psychiatric/Cognitive	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)
Psychiatric/Sexual/Decreased Function	Risperidone	1	0	18	2	16	+Inf	(0.21, Inf+)
Psychiatric/Sleep	Risperidone	3	31	110	25	104	0.78	(0.39, 1.57)
Thirst	Risperidone	1	5	52	6	49	1.31	(0.31, 5.84)
Urinary	Risperidone	1	15	52	15	49	1.09	(0.42, 2.79)

NC = Not Calculated

Table H. Autism/Tourette's studies – Atypical Antipsychotics Compared to Clondine

Adverse Events	Drug	# of studies	Clonidine		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
HEENT/Decreased Salivation	Risperidone	1	1	12	0	9	0.00	(0.00, 52.00)
Neuro	Risperidone	1	2	12	1	9	0.64	(0.01, 14.44)
Neuro/Movement Disorder/EPS	Risperidone	1	1	12	2	9	2.97	(0.13, 201.94)
Neuro/Sedation	Risperidone	1	5	12	1	9	0.19	(0.00, 2.32)

NC = Not Calculated

Table I. Autism/Tourette's studies – Atypical Antipsychotics Compared to Conventional Antipsychotics

Adverse Events	Drug	# of studies	Conventionals		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Olanzapine	1	1	6	0	6	0.00	(0.00, 39.00)
Appetite or Weight/Increase	Olanzapine	1	5	6	6	6	+Inf	(0.03, Inf+)
Appetite or Weight/Increase	Risperidone	1	20	24	22	26	1.10	(0.18, 6.75)
Cardiovascular/BP/Decrease	Olanzapine	1	1	6	0	6	0.00	(0.00, 39.00)
Dermatologic	Olanzapine	1	1	6	0	6	0.00	(0.00, 39.00)
Gastrointestinal	Olanzapine	1	0	6	2	6	+Inf	(0.19, Inf+)
HEENT/Decreased Salivation	Olanzapine	1	1	6	1	6	1.00	(0.01, 94.01)
Neuro/Fatigue	Risperidone	1	9	24	10	26	1.04	(0.29, 3.81)
Neuro/Headache	Risperidone	1	2	24	5	26	2.57	(0.37, 29.80)
Neuro/Movement Disorder	Risperidone	1	5	24	2	26	0.32	(0.03, 2.25)
Neuro/Movement Disorder/EPS	Olanzapine	1	2	6	0	6	0.00	(0.00, 5.16)
Neuro/Movement Disorder/EPS	Risperidone	1	8	24	4	26	0.37	(0.07, 1.68)
Neuro/Movement Disorder/Gait	Olanzapine	1	1	6	0	6	0.00	(0.00, 39.00)
Neuro/Movement Disorder/Tardive Dyskinesia	Olanzapine	1	0	6	0	6	NC	NC
Neuro/Sedation	Olanzapine	1	2	6	5	6	7.96	(0.43, 588.32)
Neuro/Sedation	Risperidone	1	10	24	12	26	1.20	(0.34, 4.25)
Psychiatric/Depression	Risperidone	1	6	24	8	26	1.33	(0.33, 5.68)
Psychiatric/Sleep	Olanzapine	1	0	6	1	6	+Inf	(0.03, Inf+)
Psychiatric/Sleep	Risperidone	1	7	24	1	26	0.10	(0.00, 0.90)
Trauma	Risperidone	1	6	24	1	26	0.12	(0.00, 1.16)
Urinary	Olanzapine	1	1	6	1	6	1.00	(0.01, 94.01)

NC = Not Calculated

Table J. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Placebo

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Increase	Olanzapine	5	33	575	213	580	11.16	(7.40, 17.24)
Appetite or Weight/Increase	Quetiapine	1	2	21	2	21	1.00	(0.07, 15.13)
Appetite or Weight/Increase	Risperidone	1	0	19	3	20	+Inf	(0.40, Inf+)
Appetite or Weight/Increase	Ziprasidone	1	0	92	2	210	+Inf	(0.08, Inf+)
Cardiovascular	Olanzapine	1	0	100	7	101	+Inf	(1.21, Inf+)
Cardiovascular	Ziprasidone	1	0	48	2	91	+Inf	(0.10, Inf+)
Cardiovascular/BP/Decrease	Olanzapine	1	5	377	5	370	1.02	(0.23, 4.47)
Cardiovascular/BP/Decrease	Ziprasidone	1	0	92	3	210	+Inf	(0.18, Inf+)
Cardiovascular/BP/Increase	Olanzapine	1	6	377	2	370	0.34	(0.03, 1.90)
Cardiovascular/Rhythm	Olanzapine	1	1	377	1	370	1.02	(0.01, 80.20)
Dermatologic	Ziprasidone	1	0	48	7	91	+Inf	(0.78, Inf+)
Endocrine/Diabetes	Olanzapine	2	86	10673	20	3073	0.80	(0.46, 1.32)
Endocrine/Diabetes	Quetiapine	1	85	10296	3	922	0.39	(0.08, 1.19)
Endocrine/Diabetes	Risperidone	1	85	10296	5	2860	0.21	(0.07, 0.51)
Endocrine/Prolactin	Risperidone	1	0	10	1	15	+Inf	(0.02, Inf+)
Gastrointestinal	Olanzapine	5	78	615	70	615	0.86	(0.60, 1.24)
Gastrointestinal	Quetiapine	2	10	202	43	382	2.45	(1.18, 5.61)
Gastrointestinal	Risperidone	1	0	18	1	19	+Inf	(0.02, Inf+)
Gastrointestinal	Ziprasidone	2	61	140	131	301	0.97	(0.63, 1.50)
HEENT	Ziprasidone	1	1	48	4	91	2.15	(0.21, 108.65)
HEENT/Decreased Salivation	Olanzapine	4	40	606	93	596	2.71	(1.80, 4.13)
HEENT/Decreased Salivation	Quetiapine	2	14	202	161	393	8.90	(4.93, 17.27)
HEENT/Decreased Salivation	Risperidone	1	1	6	2	10	1.23	(0.05, 88.30)
HEENT/Decreased Salivation	Ziprasidone	1	4	92	17	210	1.93	(0.61, 8.13)
HEENT/Eye	Olanzapine	1	5	100	1	101	0.19	(0.00, 1.77)
Liver Function Test Abnormality	Olanzapine	2	0	169	12	171	+Inf	(3.16, Inf+)
Liver Function Test Abnormality	Ziprasidone	1	0	48	1	91	+Inf	(0.01, Inf+)
Musculoskeletal	Quetiapine	1	0	21	1	21	+Inf	(0.03, Inf+)

NC = Not Calculated

Table J. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Placebo (continued)

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Neuro	Aripiprazol	1	14	83	6	78	0.41	(0.12, 1.22)
Neuro	Olanzapine	2	8	129	23	125	3.36	(1.38, 9.08)
Neuro	Quetiapine	2	26	202	81	393	1.81	(1.08, 3.10)
Neuro	Risperidone	1	0	6	1	10	+Inf	(0.02, Inf+)
Neuro	Ziprasidone	2	9	140	31	301	1.61	(0.72, 3.99)
Neuro/Fatigue	Olanzapine	3	20	506	55	495	2.98	(1.72, 5.35)
Neuro/Fatigue	Quetiapine	1	4	21	4	32	0.71	(0.09, 4.92)
Neuro/Fatigue	Risperidone	1	0	10	1	15	+Inf	(0.02, Inf+)
Neuro/Fatigue	Ziprasidone	1	0	48	3	91	+Inf	(0.22, Inf+)
Neuro/Headache	Olanzapine	3	94	506	68	495	0.69	(0.48, 0.98)
Neuro/Headache	Ziprasidone	2	40	140	68	301	0.72	(0.44, 1.17)
Neuro/Movement Disorder	Olanzapine	1	0	9	0	19	NC	NC
Neuro/Movement Disorder/Akathisia	Aripiprazol	1	1	83	5	78	+Inf	(1.00, Inf+)
Neuro/Movement Disorder/Akathisia	Risperidone	1	0	18	1	19	+Inf	(0.02, Inf+)
Neuro/Movement Disorder/Akathisia	Ziprasidone	2	9	140	32	301	1.69	(0.76, 4.15)
Neuro/Movement Disorder/EPS	Aripiprazol	1	1	83	0	78	NC	NC
Neuro/Movement Disorder/EPS	Olanzapine	1	0	9	1	19	+Inf	(0.01, Inf+)
Neuro/Movement Disorder/EPS	Risperidone	1	1	10	0	15	0.00	(0.00, 26.00)
Neuro/Movement Disorder/EPS	Ziprasidone	2	5	140	26	301	3.32	(1.12, 13.41)
Neuro/Movement Disorder/Tardive Dyskinesia	Olanzapine	1	0	9	0	19	NC	NC
Neuro/Pain	Olanzapine	1	3	69	8	70	2.82	(0.64, 17.24)
Neuro/Pain	Ziprasidone	2	12	140	26	301	1.02	(0.48, 2.29)
Neuro/Sedation	Aripiprazol	1	6	83	4	78	0.84	(0.16, 4.09)
Neuro/Sedation	Olanzapine	7	72	644	179	645	3.02	(2.21, 4.14)
Neuro/Sedation	Quetiapine	2	33	202	227	393	7.33	(4.69, 11.73)
Neuro/Sedation	Risperidone	3	0	35	11	45	+Inf	(2.55, Inf+)
Neuro/Sedation	Ziprasidone	2	9	140	47	301	2.64	(1.23, 6.33)

NC = Not Calculated

Table J. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Placebo (continued)

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Neuro/Speech Disorder	Quetiapine	1	0	21	1	21	+Inf	(0.03, Inf+)
Psychiatric	Olanzapine	2	15	129	6	125	0.38	(0.12, 1.09)
Psychiatric	Quetiapine	1	1	21	1	21	1.00	(0.01, 82.37)
Psychiatric/Aggression	Olanzapine	2	14	129	7	125	0.48	(0.16, 1.33)
Psychiatric/Agitation	Aripiprazol	1	9	83	5	78	0.57	(0.14, 1.99)
Psychiatric/Agitation	Olanzapine	2	31	129	18	125	0.53	(0.26, 1.05)
Psychiatric/Agitation	Ziprasidone	2	16	140	22	301	0.60	(0.29, 1.27)
Psychiatric/Anxiety	Aripiprazol	1	17	83	22	78	1.43	(0.65, 3.20)
Psychiatric/Anxiety	Olanzapine	3	67	506	62	495	0.92	(0.62, 1.37)
Psychiatric/Cognitive	Quetiapine	1	0	21	3	21	+Inf	(0.43, Inf+)
Psychiatric/Depression	Aripiprazol	1	12	83	9	78	0.75	(0.25, 2.19)
Psychiatric/Depression	Olanzapine	1	8	69	9	70	1.12	(0.36, 3.59)
Psychiatric/Irritability	Quetiapine	1	1	21	2	21	2.07	(0.10, 130.31)
Psychiatric/Mania	Aripiprazol	1	11	83	5	78	0.40	(0.09, 1.45)
Psychiatric/Mania	Quetiapine	1	7	181	9	361	0.63	(0.21, 2.04)
Psychiatric/Psychotic	Olanzapine	1	10	45	4	50	0.23	(0.04, 0.96)
Psychiatric/Self-injurious behavior	Olanzapine	1	0	9	0	19	NC	NC
Psychiatric/Sexual/Decreased Function	Quetiapine	1	0	21	1	21	+Inf	(0.03, Inf+)
Psychiatric/Sexual/Decreased Function	Risperidone	2	1	16	1	25	0.63	(0.01, 49.71)
Psychiatric/Sexual/Decreased Function	Ziprasidone	1	0	92	2	210	+Inf	(0.08, Inf+)
Psychiatric/Sleep	Aripiprazol	1	17	83	12	78	0.76	(0.30, 1.87)
Psychiatric/Sleep	Olanzapine	2	77	477	39	471	0.46	(0.30, 0.71)
Psychiatric/Sleep	Ziprasidone	2	15	140	26	301	0.74	(0.36, 1.58)
Psychiatric/Suicidal Ideation	Aripiprazol	1	0	26	0	26	NC	NC
Psychiatric/Suicidal Ideation	Olanzapine	1	0	9	0	19	NC	NC
Psychiatric/Suicidal Ideation	Risperidone	1	0	10	1	15	+Inf	(0.02, Inf+)
Pulmonary	Ziprasidone	1	2	48	8	91	2.21	(0.42, 22.18)
Urinary	Risperidone	1	0	8	1	8	+Inf	(0.03, Inf+)

NC = Not Calculated

Table K. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Conventional Antipsychotics

			Conventionals		Intervention Groups			
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Decrease	Olanzapine	1	115	636	149	1306	0.58	(0.44, 0.77)
Appetite or Weight/Increase	Aripiprazol	1	14	431	44	859	1.61	(0.85, 3.21)
Appetite or Weight/Increase	Olanzapine	2	112	768	392	1437	2.59	(2.02, 3.34)
Cardiovascular/Rhythm	Olanzapine	1	63	636	86	1306	0.64	(0.45, 0.92)
Constitutional	Olanzapine	1	36	636	45	1306	0.59	(0.37, 0.96)
Constitutional/Fever or Infection	Olanzapine	1	48	636	56	1306	0.55	(0.36, 0.84)
Endocrine/Diabetes	Olanzapine	1	7	2756	15	2703	2.19	(0.84, 6.36)
Endocrine/Diabetes	Quetiapine	1	7	2756	3	922	1.28	(0.21, 5.63)
Endocrine/Diabetes	Risperidone	1	7	2756	5	2860	0.69	(0.17, 2.52)
Gastrointestinal	Olanzapine	2	161	768	209	1437	0.60	(0.48, 0.77)
HEENT/Decreased Salivation	Olanzapine	1	103	636	290	1306	1.48	(1.15, 1.91)
HEENT/Eye	Olanzapine	1	96	636	139	1306	0.67	(0.50, 0.90)
HEENT/Increased Salivation	Olanzapine	1	124	636	113	1306	0.39	(0.29, 0.52)
Heme	Olanzapine	1	0	132	6	131	+Inf	(1.22, Inf+)
Musculoskeletal	Olanzapine	1	16	132	4	131	0.25	(0.06, 0.80)
Neuro	Aripiprazol	1	38	431	65	859	0.85	(0.55, 1.32)
Neuro/Fatigue	Olanzapine	1	104	636	150	1306	0.66	(0.50, 0.88)
Neuro/Movement Disorder	Olanzapine	1	115	636	102	1306	0.38	(0.29, 0.52)
Neuro/Movement Disorder/Akathisia	Aripiprazol	1	108	431	111	859	0.44	(0.33, 0.60)
Neuro/Movement Disorder/Akathisia	Olanzapine	2	266	768	203	1437	0.31	(0.25, 0.38)
Neuro/Movement Disorder/EPS	Aripiprazol	1	171	431	118	859	0.24	(0.18, 0.32)
Neuro/Movement Disorder/EPS	Olanzapine	2	389	768	369	1437	0.29	(0.24, 0.36)
Neuro/Movement Disorder/Gait	Olanzapine	1	20	636	22	1306	0.53	(0.27, 1.03)
Neuro/Sedation	Aripiprazol	1	32	431	43	859	0.66	(0.40, 1.09)
Neuro/Sedation	Olanzapine	1	199	636	339	1306	0.77	(0.62, 0.95)
Psychiatric	Olanzapine	1	15	636	13	1306	0.42	(0.18, 0.94)
Psychiatric/Agitation	Aripiprazol	1	30	431	53	859	0.88	(0.54, 1.45)

NC = Not Calculated

Table K. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Conventional Antipsychotics (continued)

Adverse Events	Drug	# of studies	Conventionals		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Psychiatric/Anxiety	Aripiprazol	1	50	431	108	859	1.10	(0.76, 1.60)
Psychiatric/Anxiety	Olanzapine	1	51	132	27	131	0.41	(0.22, 0.73)
Psychiatric/Lability	Olanzapine	1	7	132	10	131	1.55	(0.48, 5.45)
Psychiatric/Psychotic	Aripiprazol	1	70	431	156	859	1.14	(0.83, 1.58)
Psychiatric/Sleep	Aripiprazol	1	88	431	185	859	1.07	(0.80, 1.44)
Psychiatric/Sleep	Olanzapine	1	632	636	1122	1306	0.03	(0.01, 0.09)
Sweating	Olanzapine	1	84	636	89	1306	0.48	(0.35, 0.67)
Urinary	Olanzapine	1	39	636	47	1306	0.57	(0.36, 0.91)

NC = Not Calculated

Table L. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Mood Stabilizers

			Mood Stabilizers		Intervention Groups			
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Gastrointestinal	Quetiapine	1	0	14	2	14	+Inf	(0.19, Inf+)
HEENT	Olanzapine	1	0	126	6	125	+Inf	(1.21, Inf+)
HEENT/Decreased Salivation	Olanzapine	1	8	126	42	125	7.41	(3.22, 19.23)
Heme/Low platelets	Olanzapine	1	10	126	0	125	0.00	(0.00, 0.42)
Liver Function Test Abnormality	Olanzapine	1	0	126	6	125	+Inf	(1.22, Inf+)
Neuro	Olanzapine	1	15	126	20	125	1.41	(0.65, 3.12)
Neuro/Fatigue	Olanzapine	1	17	126	20	125	1.22	(0.57, 2.63)
Neuro/Headache	Olanzapine	2	40	340	37	342	0.91	(0.54, 1.54)
Neuro/Movement Disorder/EPS	Olanzapine	1	6	126	21	125	4.02	(1.50, 12.64)
Neuro/Pain	Olanzapine	1	18	126	17	125	0.94	(0.43, 2.06)
Neuro/Sedation	Olanzapine	2	26	340	55	342	2.81	(1.59, 5.07)
Neuro/Sedation	Quetiapine	1	0	14	2	14	+Inf	(0.19, Inf+)
Neuro/Speech Disorder	Olanzapine	1	1	126	10	125	10.79	(1.49, 475.41)
Psychiatric/Agitation	Olanzapine	1	14	126	14	125	1.01	(0.42, 2.40)
Psychiatric/Anxiety	Olanzapine	2	31	340	25	342	0.79	(0.43, 1.42)
Psychiatric/Depression	Olanzapine	1	25	214	45	217	1.97	(1.13, 3.51)
Psychiatric/Mania	Olanzapine	1	44	214	17	217	0.33	(0.17, 0.61)
Psychiatric/Sleep	Olanzapine	2	49	340	24	342	0.43	(0.25, 0.75)

NC = Not Calculated

Table M. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to SRIs

Adverse Events	Drug	# of studies	SRI		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Cardiovascular	Risperidone	1	0	10	1	10	+Inf	(0.03, Inf+)
Dermatologic	Risperidone	1	1	10	1	10	1.00	(0.01, 87.11)
Gastrointestinal	Risperidone	1	7	10	5	10	0.45	(0.05, 3.67)
Gastrointestinal	Ziprasidone	1	0	21	9	43	+Inf	(1.07, Inf+)
HEENT	Ziprasidone	1	0	21	3	43	+Inf	(0.20, Inf+)
HEENT/Decreased Salivation	Olanzapine	1	4	60	10	62	2.36	(0.61, 11.16)
HEENT/Decreased Salivation	Risperidone	1	3	10	1	10	0.28	(0.00, 4.35)
HEENT/Decreased Salivation	Ziprasidone	1	0	21	6	43	+Inf	(0.60, Inf+)
HEENT/Eye	Risperidone	1	0	10	0	10	NC	NC
HEENT/Eye	Ziprasidone	1	0	21	5	43	+Inf	(0.46, Inf+)
HEENT/Increased Salivation	Risperidone	1	0	10	0	10	NC	NC
Infections	Ziprasidone	1	0	21	5	43	+Inf	(0.46, Inf+)
Musculoskeletal	Risperidone	1	0	10	1	10	+Inf	(0.03, Inf+)
Neuro	Olanzapine	2	16	74	12	78	0.66	(0.25, 1.68)
Neuro	Risperidone	1	1	10	0	10	0.00	(0.00, 39.00)
Neuro	Ziprasidone	1	1	21	15	43	10.42	(1.38, 473.14)
Neuro/Fatigue	Olanzapine	1	5	60	11	62	3.00	(0.82, 13.75)
Neuro/Fatigue	Risperidone	1	2	10	2	10	1.00	(0.06, 17.08)
Neuro/Fatigue	Ziprasidone	1	0	21	9	43	+Inf	(1.07, Inf+)
Neuro/Headache	Risperidone	1	1	10	1	10	1.00	(0.01, 87.11)
Neuro/Movement Disorder	Olanzapine	1	0	14	0	16	NC	NC
Neuro/Movement Disorder	Risperidone	1	0	10	1	10	+Inf	(0.03, Inf+)
Neuro/Movement Disorder/Akathisia	Olanzapine	1	5	14	4	16	0.61	(0.09, 3.78)
Neuro/Movement Disorder/EPS	Risperidone	1	1	10	1	10	1.00	(0.01, 87.11)
Neuro/Movement Disorder/EPS	Ziprasidone	1	1	21	7	43	3.82	(0.44, 183.88)
Neuro/Movement Disorder/Tardive Dyskinesia	Olanzapine	1	0	14	0	16	NC	NC
Neuro/Pain	Ziprasidone	1	0	21	4	43	+Inf	(0.32, Inf+)

NC = Not Calculated

Table M. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to SRIs (continued)

Adverse Events	Drug	# of studies	SRI		Intervention Groups		Pooled OR	95% CI
			# adverse events	sample size	# adverse events	sample size		
Neuro/Sedation	Olanzapine	2	6	74	23	78	6.04	(1.95, 22.41)
Neuro/Sedation	Risperidone	1	2	10	5	10	3.72	(0.40, 53.84)
Neuro/Sedation	Ziprasidone	1	2	21	8	43	2.15	(0.37, 22.77)
Neuro/Sensory	Risperidone	1	0	10	0	10	NC	NC
Psychiatric/Agitation	Risperidone	1	0	10	0	10	NC	NC
Psychiatric/Agitation	Ziprasidone	1	0	21	9	43	+Inf	(1.07, Inf+)
Psychiatric/Anxiety	Risperidone	1	0	10	1	10	+Inf	(0.03, Inf+)
Psychiatric/Anxiety	Ziprasidone	1	2	21	0	43	0.00	(0.00, 2.55)
Psychiatric/Cognitive	Risperidone	1	1	10	0	10	0.00	(0.00, 39.00)
Psychiatric/Cognitive	Ziprasidone	1	0	21	4	43	+Inf	(0.32, Inf+)
Psychiatric/Depression	Risperidone	1	0	10	0	10	NC	NC
Psychiatric/Sexual/Decreased Function	Risperidone	1	2	10	0	10	0.00	(0.00, 5.23)
Psychiatric/Sexual/Decreased Function	Ziprasidone	1	1	21	0	43	0.00	(0.00, 19.05)
Psychiatric/Sleep	Risperidone	1	2	10	1	10	0.46	(0.01, 10.51)
Psychiatric/Sleep	Ziprasidone	1	1	21	13	43	8.45	(1.10, 386.39)
Psychiatric/Suicide Attempt	Olanzapine	1	1	14	0	16	0.00	(0.00, 34.12)
Sweating	Risperidone	1	1	10	1	10	1.00	(0.01, 87.11)
Urinary	Risperidone	1	1	10	0	10	0.00	(0.00, 39.00)

NC = Not Calculated

Table N. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to Tricyclic Antidepressants

			Tricyclic Antidepressants		Intervention Groups			
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Cardiovascular/BP/Decrease	Olanzapine	1	10	20	4	20	0.26	(0.05, 1.21)
Endocrine/Prolactin	Olanzapine	1	1	20	6	20	7.76	(0.80, 393.79)

NC = Not Calculated

Table O. Depression/OCD/PD/PTSD studies – Atypical Antipsychotics Compared to SNRIs

			SNRI		Intervention Groups			
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Neuro/Fatigue	Olanzapine	1	5	59	11	62	2.94	(0.81, 13.51)
Neuro/Sedation	Olanzapine	1	5	59	11	62	2.94	(0.81, 13.51)

NC = Not Calculated

Table P. Depression/OCD/PD/PTSD studies – Atypical Antipsychotic Compared to Another Atypical Antipsychotic

Adverse Events	Atypical antipsychotic 1	Atypical antipsychotic 2	# of studies	Atypical antipsychotic 1		Atypical antipsychotic 2		Pooled OR	95% CI
				# adverse events	sample size	# adverse events	sample size		
Appetite or Weight/Decrease	Risperidone	Quetiapine	1	0	175	4	553	+Inf	(0.21, Inf+)
Appetite or Weight/Decrease	Ziprasidone	Olanzapine	1	10	192	2	202	0.18	(0.02, 0.87)
Appetite or Weight/Increase	Risperidone	Quetiapine	1	6	175	14	553	0.73	(0.26, 2.36)
Appetite or Weight/Increase	Ziprasidone	Olanzapine	1	19	192	62	202	4.02	(2.25, 7.48)
Cardiovascular	Ziprasidone	Olanzapine	2	7	328	16	335	2.39	(0.91, 7.01)
Constitutional	Ziprasidone	Olanzapine	1	52	136	39	133	0.67	(0.39, 1.15)
Constitutional/Fever or Infection	Ziprasidone	Olanzapine	1	5	192	0	202	0.00	(0.00, 1.42)
Dermatologic	Ziprasidone	Olanzapine	1	14	136	10	133	0.71	(0.27, 1.79)
Endocrine	Ziprasidone	Olanzapine	1	6	136	14	133	2.54	(0.88, 8.34)
Endocrine/Diabetes	Quetiapine	Olanzapine	1	3	922	15	2703	1.71	(0.70, 5.03)
Endocrine/Diabetes	Risperidone	Olanzapine	1	5	2860	15	2703	3.19	(1.10, 11.22)
Endocrine/Diabetes	Risperidone	Quetiapine	1	5	2860	3	922	1.86	(0.29, 9.60)
Gastrointestinal	Ziprasidone	Olanzapine	2	76	328	57	335	0.66	(0.43, 1.00)
HEENT/Bruxism	Ziprasidone	Olanzapine	1	4	192	0	202	0.00	(0.00, 1.42)
HEENT/Decreased Salivation	Risperidone	Quetiapine	1	12	175	80	553	2.30	(1.20, 4.75)
HEENT/Decreased Salivation	Ziprasidone	Olanzapine	1	20	192	32	202	1.56	(0.82, 3.01)
Heme	Ziprasidone	Olanzapine	1	3	136	5	133	1.73	(0.33, 11.36)
Musculoskeletal	Ziprasidone	Olanzapine	1	8	136	8	133	1.02	(0.32, 3.24)
Neuro	Risperidone	Quetiapine	1	12	175	70	553	1.97	(1.02, 4.09)
Neuro/Headache	Risperidone	Quetiapine	1	11	175	52	553	1.55	(0.77, 3.37)
Neuro/Headache	Ziprasidone	Olanzapine	1	25	192	32	202	1.21	(0.66, 2.24)
Neuro/Movement Disorder	Ziprasidone	Olanzapine	1	0	192	5	202	+Inf	(0.88, Inf+)
Neuro/Movement Disorder/EPS	Risperidone	Quetiapine	1	75	175	227	553	0.92	(0.64, 1.31)
Neuro/Sedation	Risperidone	Quetiapine	1	27	175	173	553	2.49	(1.57, 4.06)
Neuro/Sensory	Ziprasidone	Olanzapine	1	8	136	6	133	0.76	(0.21, 2.57)
Psychiatric/Agitation	Risperidone	Quetiapine	1	3	175	34	553	3.75	(1.16, 19.33)
Psychiatric/Anxiety	Ziprasidone	Olanzapine	1	82	136	64	133	0.61	(0.37, 1.02)
Psychiatric/Irritability	Ziprasidone	Olanzapine	1	7	192	2	202	0.26	(0.03, 1.42)
Psychiatric/Psychotic	Ziprasidone	Olanzapine	1	15	192	5	202	0.30	(0.08, 0.89)

NC = Not Calculated

Table P. Depression/OCD/PD/PTSD studies – Atypical Antipsychotic Compared to Another Atypical Antipsychotic (continued)

Adverse Events	Atypical antipsychotic 1	Atypical antipsychotic 2	# of studies	Atypical antipsychotic 1		Atypical antipsychotic 2		Pooled OR	95% CI
				# adverse events	sample size	# adverse events	sample size		
Psychiatric/Sleep	Risperidone	Quetiapine	1	17	175	65	553	1.24	(0.69, 2.32)
Psychiatric/Sleep	Ziprasidone	Olanzapine	1	35	192	25	202	0.66	(0.36, 1.19)
Pulmonary	Ziprasidone	Olanzapine	1	24	136	16	133	0.64	(0.30, 1.33)
Urinary	Ziprasidone	Olanzapine	1	9	136	5	133	0.55	(0.14, 1.90)

NC = Not Calculated

Table Q. Depression/OCD/PD/PTSD studies – Olanzapine with Fluoxetine Comapred to Fluoxetine

		Fluoxetine		Olanzapine + Fluoxetine			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Neuro	1	0	14	1	15	+Inf	(0.02, +Inf)
Neuro/Movement Disorder	1	0	14	0	15	NC	NC
Neuro/Movement Disorder/Akathisia	1	5	14	5	15	0.90	(0.15, 5.44)
Neuro/Movement Disorder/Tardive Dyskinesia	1	0	14	0	15	NC	NC
Neuro/Sedation	1	3	14	7	15	3.08	(0.50, 24.41)
Psychiatric/Suicide Attempt	1	1	14	0	15	0.00	(0.00, 36.40)

NC = Not Calculated

Table R. Depression/OCD/PD/PTSD studies – Quetiapine with Paraxetine Compared to Paraxetine

		Paroxetine		Quetiapine + Paraxetine			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Increase	1	1	54	12	58	12.22	(1.66, 545.28)
Psychiatric/Anxiety	1	7	54	1	58	0.12	(0.00, 0.98)
Psychiatric/Sleep	1	17	54	0	58	0.00	(0.00, 0.18)

NC = Not Calculated

Table S. Depression/OCD/PD/PTSD studies – Risperidone with Paraxetine Compared to Paraxetine

		Paroxetine		Risperidone + Paroxetine			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Decrease	1	1	10	0	10	0.00	(0.00, 39.00)
Appetite or Weight/Increase	1	3	10	6	10	3.27	(0.41, 33.28)
Cardiovascular	1	0	10	0	10	NC	NC
Dermatologic	1	1	10	0	10	0.00	(0.00, 39.00)
Gastrointestinal	1	7	10	3	10	0.20	(0.02, 1.68)
HEENT/Decreased Salivation	1	3	10	1	10	0.28	(0.00, 4.35)
HEENT/Eye	1	0	10	1	10	+Inf	(0.03, +Inf)
HEENT/Increased Salivation	1	0	10	1	10	+Inf	(0.03, +Inf)
Musculoskeletal	1	0	10	0	10	NC	NC
Neuro	1	1	10	1	10	1.00	(0.01, 87.11)
Neuro/Fatigue	1	2	10	1	10	0.46	(0.01, 10.51)
Neuro/Headache	1	1	10	0	10	0.00	(0.00, 39.00)
Neuro/Movement Disorder	1	0	10	0	10	NC	NC
Neuro/Movement Disorder/EPS	1	1	10	1	10	1.00	(0.01, 87.11)
Neuro/Sedation	1	2	10	2	10	1.00	(0.06, 17.08)
Neuro/Sensory	1	0	10	1	10	+Inf	(0.03, +Inf)
Psychiatric/Agitation	1	0	10	1	10	+Inf	(0.03, +Inf)
Psychiatric/Anxiety	1	0	10	0	10	NC	NC
Psychiatric/Cognitive	1	1	10	1	10	1.00	(0.01, 87.11)
Psychiatric/Depression	1	0	10	1	10	+Inf	(0.03, +Inf)
Psychiatric/Sexual/Decreased Function	1	2	10	3	10	1.67	(0.14, 25.60)
Psychiatric/Sleep	1	2	10	1	10	0.46	(0.01, 10.51)
Sweating	1	1	10	0	10	0.00	(0.00, 39.00)
Urinary	1	1	10	0	10	0.00	(0.00, 39.00)

NC = Not Calculated

Table T. Depression/OCD/PD/PTSD studies – Risperidone with SRI Compared to SRI

		SRI		Risperidone vs SRI			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Increase	1	3	16	6	20	1.83	(0.31, 13.66)
Cardiovascular/Rhythm	1	1	16	0	20	0.00	(0.00, 31.20)
Gastrointestinal	1	1	16	1	20	0.79	(0.01, 66.06)
HEENT/Decreased Salivation	1	5	16	5	20	0.74	(0.13, 4.10)
HEENT/Eye	1	2	16	0	20	0.00	(0.00, 4.19)
Neuro	1	5	16	3	20	0.40	(0.05, 2.54)
Neuro/Headache	1	5	16	0	20	0.00	(0.00, 0.75)
Neuro/Movement Disorder/EPS	1	1	16	0	20	0.00	(0.00, 31.20)
Neuro/Sedation	1	8	16	17	20	5.37	(0.96, 40.18)
Psychiatric/Agitation	1	6	16	6	20	0.72	(0.14, 3.60)
Psychiatric/Sleep	1	1	16	1	20	0.79	(0.01, 66.06)
Sweating	1	4	16	1	20	0.17	(0.00, 1.94)
Urinary	1	0	16	1	20	+Inf	(0.02, +Inf)

NC = Not Calculated

Table U. Depression/OCD/PD/PTSD studies – Quetiapine with SRI Compared to SRI

		SRI		Quetiapine + SRI			
Adverse Events	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI
Appetite or Weight/Increase	1	0	20	10	20	+Inf	(3.43, +Inf)
Cardiovascular/Rhythm	1	2	20	0	20	0.00	(0.00, 5.28)
Gastrointestinal	2	2	33	6	34	3.36	(0.52, 38.17)
HEENT/Decreased Salivation	1	8	20	11	20	1.81	(0.44, 7.73)
Neuro	2	0	33	7	34	+Inf	(1.66, +Inf)
Neuro/Fatigue	1	0	20	2	20	+Inf	(0.19, +Inf)
Neuro/Headache	1	1	13	0	14	0.00	(0.00, 36.21)
Neuro/Pain	1	0	20	2	20	+Inf	(0.19, +Inf)
Neuro/Sedation	2	9	33	22	34	9.32	(2.16, 58.89)
Psychiatric	1	3	20	2	20	0.64	(0.05, 6.29)
Psychiatric/Anxiety	1	1	13	0	14	0.00	(0.00, 36.21)
Psychiatric/Cognitive	1	0	20	3	20	+Inf	(0.43, +Inf)
Psychiatric/Sleep	1	0	20	2	20	+Inf	(0.19, +Inf)
Sweating	1	6	20	2	20	0.27	(0.02, 1.80)

NC = Not Calculated