Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults

A Systematic Review and Meta-analysis

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Context Atypical antipsychotic medications are commonly used for off-label conditions such as agitation in dementia, anxiety, and obsessive-compulsive disorder.

Objective To perform a systematic review on the efficacy and safety of atypical antipsychotic medications for use in conditions lacking approval for labeling and marketing by the US Food and Drug Administration.

Data Sources and Study Selection Relevant studies published in the English language were identified by searches of 6 databases (PubMed, EMBASE, CINAHL, PsycInfo, Cochrane DARE, and CENTRAL) from inception through May 2011. Controlled trials comparing an atypical antipsychotic medication (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, iloperidone, or paliperidone) with placebo, another atypical antipsychotic medication, or other pharmacotherapy for adult off-label conditions were included. Observational studies with sample sizes of greater than 1000 patients were included to assess adverse events.

Data Extraction Independent article review and study quality assessment by 2 investigators.

Data Synthesis Of 12 228 citations identified, 162 contributed data to the efficacy review. Among 14 placebo-controlled trials of elderly patients with dementia reporting a total global outcome score that includes symptoms such as psychosis, mood alterations, and aggression, small but statistically significant effects sizes ranging from 0.12 and 0.20 were observed for aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, a pooled analysis of 3 trials showed that quetiapine was associated with a 26% greater likelihood of a favorable response (defined as at least 50% improvement on the Hamilton Anxiety Scale) compared with placebo. For obsessive-compulsive disorder, risperidone was associated with a 3.9-fold greater likelihood of a favorable response (defined as a 25% improvement on the Yale-Brown Obsessive Compulsive Scale) compared with placebo. In elderly patients, adverse events included an increased risk of death (number needed to harm [NNH]=87), stroke (NNH=53 for risperidone), extrapyramidal symptoms (NNH=10 for olanzapine; NNH=20 for risperidone), and urinary tract symptoms (NNH range=16-36). In nonelderly adults, adverse events included weight gain (particularly with olanzapine), fatigue, sedation, akathisia (for aripiprazole), and extrapyramidal symptoms.

Conclusions Benefits and harms vary among atypical antipsychotic medications for off-label use. For global behavioral symptom scores associated with dementia in elderly patients, small but statistically significant benefits were observed for aripiprazole, olanzapine, and risperidone. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder, and risperidone was associated with benefits in the treatment of obsessive-compulsive disorder; however, adverse events were common.

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Atypical antipsychotic medications are approved for marketing and labeling by the US Food and Drug Administration (FDA) for treating schizophrenia, bipolar disorder, and depression under drug-specific circumstances. The use of atypical antipsychotic medications is rapidly increasing in the United States, with 1 study estimating an increase from 6.2 million to 14.3 million treatment visits between 1995 and 2008. The estimated use of these drugs for off-label indications, meaning those without FDA approval for these indications, doubled during this period.[1] The most commonly prescribed atypical antipsychotic medications are quetiapine, risperidone, aripiprazole, and olanzapine.[1] Other atypical antipsychotic medications include asenapine, clozapine, iloperidone, paliperidone, and ziprasidone.

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This review summarizes the efficacy and adverse events associated with off-label use of atypical antipsychotic medications for behavioral symptoms in dementia, anxiety, obsessive-compulsive disorder (OCD), eating disorders, posttraumatic stress disorder (PTSD), insomnia, personality disorders, depression, and substance abuse. Off-label prescribing of atypical antipsychotic medications most commonly occurs for adults with these conditions.[2] We assessed both efficacy (comparisons of an atypical antipsychotic medication with a placebo) and comparative effectiveness (studies comparing one atypical antipsychotic medication with another active medication).

METHODS

The complete methods are provided in the evidence report.[2] A protocol for this review is available online.[3] We searched PubMed, EMBASE, CINAHL, PsycInfo, Cochrane DARE, and CENTRAL through May 2011 for studies of atypical antipsychotic medications including aripiprazole, asenapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Clozapine was excluded due to its almost exclusive use for schizophrenia. Search terms included the drug names and terms for the conditions previously described. We included depression for drugs without FDA approval for this indication. Regulatory documents from the FDA and Health Canada were searched. We performed reference mining of relevant reviews. We included only studies published in the English language. Clinical trials were used to assess efficacy outcomes. Adverse events were abstracted from clinical trials and large observational studies.

Relevant outcomes were selected by expert psychiatrists. Four investigators (A.R.M., M.M., J.-H.H., and Z.W.) independently reviewed titles and abstracts for potentially relevant articles. These investigators abstracted data from the full-text articles using structured review forms and disagreements were resolved by consensus. Statisticians abstracted outcome data (verified by a clinician-investigator) for the pooled analyses. One investigator (M.S.) abstracted data on adverse events; these data were checked by a second reviewer (A.R.M.).

To assess internal validity of the clinical trials, we abstracted data on the adequacy of the randomization method, the adequacy of blinding and allocation concealment, and the reporting of patients lost to follow-up. The Jadad scale[4] (score range, 0-5; 5 = best score) was used to quantify the quality of the clinical trials. The Newcastle-Ottawa Scale[5] was used to assess internal validity of observational studies.

For studies reporting a continuous outcome, effect sizes were calculated for each comparison. For subgroups involving data pooling across several scales, we calculated a standardized mean difference using the Hedges effect size. Effect sizes of 0.20 or less were considered small and effect sizes of 0.50 or greater were considered large.[6] For efficacy outcomes that reported the number of events, relative risks (RRs) were calculated. The strength of the evidence was assessed using criteria from the Evidence-based Practice Centers Program,[7] which was modeled on the Grading of Recommendations Assessment, Development, and Evaluation system.[8] The strength of the evidence was classified as high, moderate, or low and considered 4 primary domains (risk of bias, consistency of effect, directness of evidence, and precision of the result) as well as secondary domains that included the strength of the association and the potential for publication bias.

The ability to pool the data across studies was determined by the project team. In the dementia studies, we generally used the Neuropsychiatric Inventory (NPI) total score for the total global outcome, the NPI psychosis scale for the psychosis outcome, and the Cohen-Mansfield agitation inventory for the agitation outcome. If these scales were not included in a study, results from alternative psychiatric and behavioral measures were used. For other conditions, we used standard outcome scales such as the Yale-Brown Obsessive Compulsive Scale. At least 3 studies were required for an efficacy meta-analysis.

For trials that were sufficiently clinically similar to warrant meta-analysis, we calculated a pooled random-effects estimate of the overall effect size or an RR for efficacy outcome measures. The individual trial outcomes were weighted by both within-study and between-study variation. For adverse events that occurred in 2 or more trials, we used exact conditional inference to estimate the pooled odds ratio (OR).

We assessed publication bias using the Begg adjusted rank correlation test and the Egger regression asymmetry test. Heterogeneity was assessed using the I^2 statistic. The number needed to treat was calculated for significant RRs. To calculate the number needed to treat, we used the pooled RR and the assumed control risk from the placebo group. Analogous methods were used to calculate the number needed to harm (NNH).

All meta-analyses were conducted using Stata statistical software version 10.0 (StataCorp, College Station, Texas) and StatXact Procs version 9 (Cytel Software Corporation, Cambridge, Massachusetts).

RESULTS

Our searches identified 12 228 titles, of which 2066 articles underwent full text review. This study included 162 trials with efficacy outcomes and 231 trials or large observational studies with adverse events (eSupplement and eFigure at http://www.jama.com). We did not find any relevant trials of asenapine, iloperidone, or paliperidone.

Psychosis, Agitation, and Global Behavioral Symptoms in Dementia

Efficacy. Prior systematic reviews and meta-analyses found either small but statistically significant effects for some atypical antipsychotic medications but not others,[9-11] or no statistically significant benefits[12] for treatment of behavioral symptoms in dementia. We iden-

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tified 38 eligible trials,[13-36] including 13 trials[37-50] that were not included in prior systematic reviews. The mean sample size was 238 (range, 16-815). Follow-up ranged from 2 days to 1 year. Trial quality ranged from 0 to 5 on the Jadad scale.

Eighteen placebo-controlled trials* reported outcomes between 6 and 12 weeks of follow-up and were included in the pooled analyses. We examined 3 types of outcomes: improvement in psychosis (delusions and hallucinations, principally), improvement in agitation (including physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor activity), and a total global score, which included cumulative psychiatric symptoms of delusions, hallucinations, suspiciousness, dysphoria, anxiety, motor agitation, aggression, hostility, euphoria, disinhibition, irritability, apathy, and other behavioral disturbances. The details of these studies appear in the evidence report.[2]

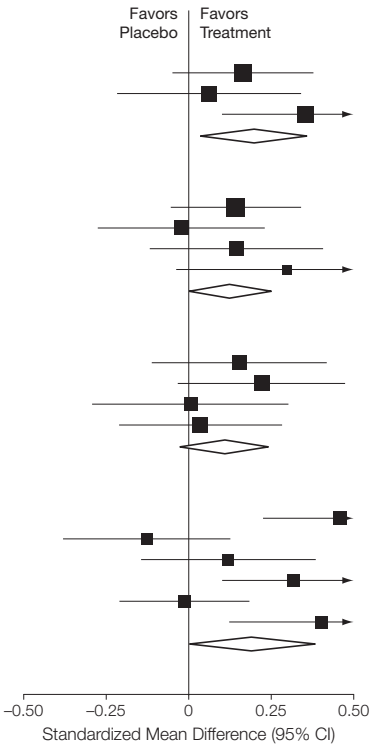
Most of the studies used flexible dosing schedules that ranged from 2 to 15 mg/d for aripiprazole, 1 to 15 mg/d for olanzapine, 25 to 600 mg/d for quetiapine, and 0.5 to 2.5 mg/d for risperidone. Results of our pooled analysis for the total global scores are presented in FIGURE 1.[52-55] For aripiprazole, olanzapine, and risperidone, the pooled estimate of the effect size was small but statistically significant (range, 0.12-0.20). The pooled estimate of effect for quetiapine was similar (0.11) but was not statistically different than zero. Consistent with these findings, the mean change in the NPI total score in patients treated with an antipsychotic medication was a 35% improvement compared with baseline, while the difference in the pooled NPI total score between treatment and placebo was 3.41 points. These values are slightly above and below (respectively) the thresholds for 30% improvement (compared with baseline) and 4-point improvement (compared with placebo) that are considered to be the minimum clinically observable change.[56] The findings together are consistent with the conclusion that the effect size for atypical antipsychotic medications is on average a small improvement in global symptoms.

We classified the strength of evidence for this outcome as high based on the number and size of the trials, their quality, and the consistency of their results. Individual studies suggested

*References 14-18, 23, 25, 26, 28-32, 39, 43, 46, 48, 51.

Figure 1. Controlled Trials of Patients Taking Atypical Antipsychotic Medications vs Placebo

Source	Dose, mg/d	Standardized Mean Difference (95% CI)
Aripiprazole		
Mintzer et al,[14] 2007	2, 5, 10	0.16 (–0.05 to 0.37)
De Deyn et al,[16] 2003[a]	10 (mean)	0.06 (–0.21 to 0.34)
Streim et al,[53] 2004 and Streim et al,[15] 2008	8.6 (mean)	0.36 (0.11 to 0.61)
Subtotal		0.20 (0.04 to 0.35)
I^2 = 22.1%; P = .28		
Olanzapine		
De Deyn et al,[18] 2004	1, 2.5, 5, 7.5	0.14 (–0.05 to 0.34)
Deberdt et al,[23] 2005	5.2 (mean)	–0.02 (–0.27 to 0.23)
Schneider et al,[52] 2006 and Sultzer et al,[26] 2008	5.5 (mean)	0.15 (–0.11 to 0.40)
Street et al,[17] 2000	5, 10, 15	0.30 (–0.03 to 0.63)
Subtotal		0.12 (0 to 0.25)
I^2 = 0%; P = .49		
Quetiapine		
Schneider et al,[52] 2006 and Sultzer et al,[26] 2008	56.5 (mean)	0.15 (–0.11 to 0.42)
Tariot et al,[29] 2002[a]	97 (median)	0.22 (–0.03 to 0.47)
Tariot et al,[46] 2006	96.9 (median)	0 (–0.29 to 0.30)
Zhong et al,[54] 2004 and Zhong et al,[39] 2007	100, 120, 200	0.04 (–0.21 to 0.28)
Subtotal		0.11 (–0.02 to 0.24)
I^2 = 0%; P = .63		
Risperidone		
Brodaty et al,[31] 2003 and Brodaty et al,[55] 2005	0.95 (mean)	0.46 (0.23 to 0.69)
Deberdt et al,[23] 2005	1 (mean)	–0.13 (–0.38 to 0.12)
De Deyn et al,[30] 1999	1.1 (mean)	0.12 (–0.14 to 0.38)
Katz et al,[32] 1999	0.5, 1.2	0.32 (0.11 to 0.53)
Mintzer et al,[48] 2006	1.03 (mean)	–0.01 (–0.21 to 0.18)
Schneider et al,[52] 2006 and Sultzer et al,[26] 2008	1 (mean)	0.40 (0.13 to 0.68)
Subtotal		0.19 (0 to 0.38)
I^2 = 74.6%; P = .001		



Total global scores are presented and include the symptoms of delusion, hallucination, dysphoria, anxiety, agitation or aggression, euphoria, disinhibition, irritability, apathy, aberrant motor activity, and behavioral disturbances. Weights are from a random-effects analysis. The size of the data markers is proportional to the sample size of the trial.

[a] The data used for this study were abstracted from the meta-analysis by Schneider et al.[10]

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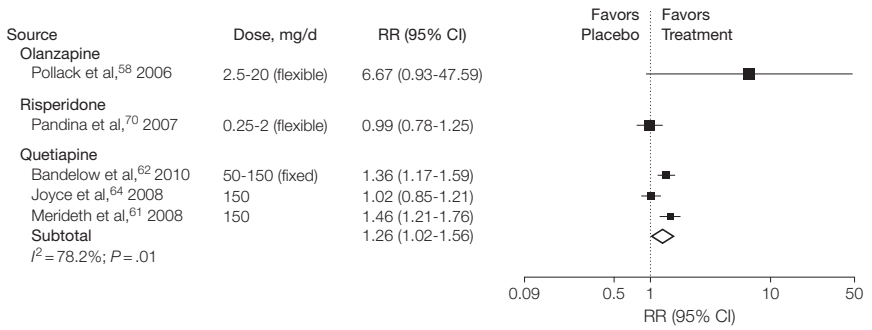
Figure 2. Controlled Trials of Patients With Anxiety Taking Atypical Antipsychotic Medications vs Placebo



Improvement in anxiety determined using the Hamilton Anxiety Rating Scale. Weights are from a random-effects analysis. The size of the data markers is proportional to the sample size of the trial. RR indicates relative risk.

that higher doses of aripiprazole (10 mg/d)[14] or risperidone (2 mg/d)[32] may be more effective than lower doses. However, these findings have not been replicated, dose effects are not addressed in most trials, and dose-response trends are inconsistent across studies. The pooled analysis for risperidone had substantial heterogeneity (I^2=74.6%). There was no evidence of publication bias.

For the outcome of psychosis, the pooled effect size was 0.20 (95% CI, 0.05 to 0.36) for risperidone (5 trials), 0.20 (95% CI, –0.02 to 0.42) for aripiprazole (3 trials), 0.05 (95% CI, –0.07 to 0.17) for olanzapine (5 trials), and –0.03 (95% CI, –0.24 to 0.18) for quetiapine (3 trials). Aripiprazole, olanzapine, and risperidone were all associated with statistically significant improvement in agitation (range of pooled effect sizes, 0.19 to 0.31). The pooled effect for quetiapine was 0.05 (95% CI, –0.14 to 0.25). Details of these analyses are presented in our evidence report.[2]

Comparative Effectiveness. Three trials compared risperidone with olanzapine[23,26] or risperidone with quetiapine.[26,38] There were no significant differences in these comparisons. Five trials[30,40,41,46,47] compared an atypical antipsychotic medication with haloperidol for the total global outcome. The results were inconsistent. Some trials reported statistically significant results favoring haloperidol,[46] others reported results favoring the atypical antipsychotic medication,[40,41] and some trials reported no statistically significant differences.[30,47]

Generalized Anxiety Disorder

Efficacy. One prior systematic review[57] reported that quetiapine monotherapy was superior to placebo. We identified 14 trials evaluating olanzapine,[58] quetiapine,[59-67] risperidone,[68-70] or ziprasidone[71] for treatment of generalized anxiety disorder. Most used flexible dosing schedules. Sample sizes ranged from 12 to 951 patients. Clinical trial quality scores ranged from 2 to 5 on the Jadad scale. Twelve trials were placebo-controlled with a mean follow-up of 6 to 18 weeks. Of these, 5 reported the percentage of patients responding based on an improvement in the Hamilton Anxiety (HAM-A) Rating Scale score of at least 50%. These trials are shown in FIGURE 2.

One small trial (n=24) reported results favoring treatment with 2.5 to 20 mg/d of olanzapine, but this finding was not statistically significant.[58] One trial[70] with dose ranges of 0.25 to 2 mg/d of risperidone showed no statistically or clinically significant results. Three large trials (n=710, n=854, and n=873) assessed quetiapine.[61,62,64] The pooled result of these quetiapine trials was a 26% increase in the chance of a favorable response at 8 weeks (number needed to treat=8). This is approximately equivalent to an effect size of 0.30. Doses of quetiapine ranged from 50 to 300 mg/d. The I^2 for the quetiapine analysis was 78.2% (P=.01), which indicates unexplained heterogeneity. There was no evidence of publication bias. We classified the strength of evidence for this outcome as moderate based on the inconsistency of results and because all were funded by manufacturers.

One study of ziprasidone,[71] 6 studies of quetiapine,[59,60,63,65-67] and 2 studies of risperidone[68,69] reported results that could not be pooled. The flexible-dose (20-80 mg/d) ziprasidone study reported no difference compared with placebo in HAM-A scores at 8 weeks.[71] The flexible-dose (0.5-1.5 mg/d) risperidone study (n=40) reported better improvements in HAM-A scores at 8-week follow-up when low-dose risperidone was used adjunctively in patients without an adequate response to 4 weeks of standard treatment.[69] A study on anxiety in patients with bipolar disorder found that risperidone was no more effective than placebo.[68] The 6 quetiapine studies represented heterogeneous trials assessing the ability of quetiapine to improve response to selective serotonin reuptake inhibitors (SSRIs),[59,60,66,67] the treatment of anxiety in patients with bipolar disorder,[63] and the use of quetiapine for maintenance therapy.[65] Doses of quetiapine ranged from 25 to 600 mg/d. The results were inconclusive.

Comparative Effectiveness. No studies that directly compared atypical antipsychotic medications for treating generalized anxiety disorder were identified. One trial compared 50 or 150 mg/d of quetiapine with 20 mg/d of paroxetine,[62] while another compared 150 or 300 mg/d of quetiapine with 10 mg/d of escitalopram.[61] Quetiapine was equally effective as paroxetine at 8 weeks, with fewer reported sexual adverse effects. Both quetiapine and escitalopram were effective at 8 weeks.

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Obsessive-Compulsive Disorder

Efficacy. Four prior meta-analyses assessed various atypical antipsychotic medications either singly (eg, quetiapine alone) or as a class. These analyses generally concluded that there was statistically significant evidence of benefit. We identified 16 trials[72-87] of atypical antipsychotic medications as treatment for OCD, of which 6 trials[82-87] were not included in prior systematic reviews. Ten were placebo-controlled trials of an atypical antipsychotic medication as augmentation therapy for patients with OCD who did not respond to SSRIs. Sample sizes ranged from 16 to 82 patients. Follow-up times ranged from 6 weeks to 6 months. Quality varied from 1 to 5 on the Jadad scale. All studies assessed outcomes using the proportion of patients responding as measured by the Yale-Brown Obsessive Compulsive Scale (response varied from an improvement of 25%-35%). The results are presented in FIGURE 3.

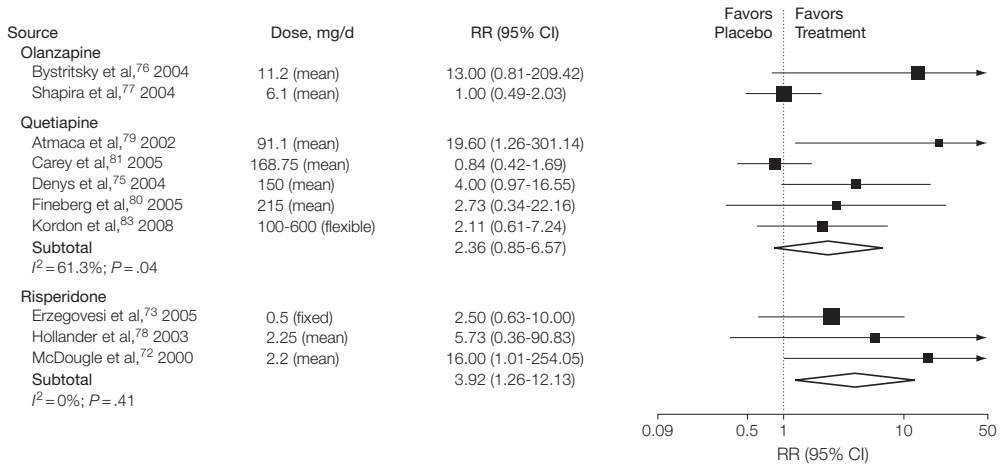
Two studies of olanzapine found no statistically significant difference compared with placebo (mean daily doses: 11.2 and 6.1 mg). Five studies assessing doses of between 90 mg/d and 600 mg/d of quetiapine were pooled. While the pooled results favored treatment with quetiapine, these were not statistically significant. The I^2 for the quetiapine analysis was 61.3% ($P = .04$), which indicates unexplained heterogeneity. Three pooled studies of risperidone resulted in an approximate 4-fold increase in the chance of responding compared with placebo (the number needed to treat: 5). This is approximately equivalent to an effect size of 1.14. Doses ranged from 0.5 to 2.25 mg/d. Both the Begg and Egger tests indicated the possibility of publication bias ($P = .002$ for both). We classified the strength of evidence for this outcome as moderate based on the potential for publication bias. Two other trials evaluated the treatment of OCD with 300 to 450 mg/d of quetiapine plus citalopram or placebo plus citalopram.[85,87] These studies found that quetiapine augmentation was superior to placebo.

Comparative Effectiveness. We identified 1 trial[82] of SSRI augmentation that compared treatment with 2.5 to 10 mg/d of olanzapine with 1 to 3 mg/d of risperidone. There were no statistically significant differences between the treatment groups. Another trial[84] compared an atypical antipsychotic medication plus an SSRI plus cognitive behavioral therapy for the treatment of OCD with an SSRI plus cognitive behavioral therapy (but no atypical antipsychotic medication). Those receiving the atypical antipsychotic medication were treatment resistant and sicker than the other group, and had a mean reduction in Yale-Brown Obsessive Compulsive Scale score of 10 points. One small trial compared quetiapine (dose: 50-200 mg/d) plus an SSRI with clomipramine (25-75 mg/d) plus an SSRI.[86] Quetiapine augmentation was associated with a significant decline in the Yale-Brown Obsessive Compulsive Scale score, while clomipramine augmentation was not.

Other Conditions

We identified 5 trials of olanzapine and 1 of quetiapine for eating disorders, 12 trials for personality disorder, 1 existing meta-analysis and 10 trials of risperidone or olanzapine for PTSD, and 36 trials of atypical antipsychotic medications for depression, of which 7 trials assessed drugs without an FDA-approved indication and 33 trials assessed aripiprazole, olanzapine, quetiapine, or risperidone for treating substance abuse disorders. We identified 1 small trial (n = 13) of atypical an-

Figure 3. Controlled Trials of Patients With Obsessive-Compulsive Disorder Taking Atypical Antipsychotic Medications vs Placebo



Improvement in obsessive compulsive disorder determined using the Yale-Brown Obsessive Compulsive Scale. Weights are from a random-effects analysis. RR indicates relative risk. The size of the data markers is proportional to the sample size of the trial.

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tipsychotic medications for insomnia, which was inconclusive (eReferences at http://www.jama.com).

Details for these conditions are presented in the evidence report.[2] Evidence does not support the use of olanzapine for eating disorders. The level of evidence is mixed regarding personality disorders and is moderate for an association of risperidone with improving PTSD. Evidence does not support the use of atypical antipsychotic medications for substance abuse.

Adverse Events

We considered adverse events in 2 categories: elderly patients with dementia and all other nonelderly adult patients. Adverse events were grouped by drug within age category and then across conditions.

Elderly Patients With Dementia. In 2005, the FDA issued a public health advisory for treating behavioral disturbances in dementia with atypical antipsychotic medications after studies reported an increased risk of death. In 15 placebo-controlled trials, death occurred in 3.5% of patients randomized to atypical antipsychotic medications compared with 2.3% of patients randomized to placebo. The pooled OR for death was 1.54 (95% CI, 1.06-2.23; NNH=87).[88] We also identified 2 large high-quality cohort studies that reported higher mortality in patients taking atypical antipsychotic medications compared with those not taking these drugs.[89,90] We combined data from placebo-controlled trials in a meta-analysis on cardiovascular symptoms, edema, and vasodilatation. These outcomes were significantly more common in patients taking olanzapine and risperidone compared with placebo. Quetiapine and aripiprazole were not associated with cardiovascular outcomes (Table 1). Risperidone (not olanzapine, aripiprazole, or quetiapine) was associated with an increased risk of stroke (pooled OR, 3.12 [95% CI, 1.32-8.21]; NNH=53). The numbers of trials and patients were small and the 95% CIs were wide.

Our meta-analysis found that olanzapine (pooled OR, 4.70 [95% CI, 1.87-14.14]; NNH=24) and risperidone (pooled OR, 3.40 [95% CI, 1.08-12.75]; NNH=25) were associated with increases in appetite and weight. Only one trial[48] studied the association of these drugs with the development of diabetes in elderly patients; this trial showed no difference between risperidone and placebo. One study[25] of olanzapine showed significantly greater central and peripheral anticholinergic effects (OR, 3.30 [95% CI, 1.62-7.17]; NNH=6) compared with placebo. Aripiprazole, olanzapine, quetiapine, and risperidone were each associated with sedation and fatigue in patients with dementia. Olanzapine and risperidone were associated with an increase in extrapyramidal symptoms (NNH=10 and 20, respectively). Risperidone, quetiapine, and olanzapine were associated with increases in urinary tract symptoms (Table 1; NNH range: 16-36). A large government-funded trial (Clinical Antipsychotic Trial of Intervention Effectiveness Study for Alzheimer's Disease[91]; CATIE-AD) comparing olanzapine, quetiapine, and risperidone reported cognitive decline in patients with dementia who were treated with these drugs.

Comparative Harms. We found 6 head-to-head trials of atypical antipsychotic medications for dementia that reported adverse events, including the CATIE-AD trial.[52] Patients taking olanzapine had greater odds of having a neurological symptom such as confusion, dizziness, headaches, lightheadedness, orthostatic dizziness, seizure, or tinnitus than those taking risperidone (OR, 1.54; 95% CI, 1.02-2.34). Of 6 large high-quality cohort studies, 4 found an increased risk of death with conventional antipsychotic medications compared with atypical antipsychotic medications.[89,92-94] The remaining 2 cohort studies[90,95] found a similar risk of death in the comparison between use of conventional antipsychotic medications and use of atypical antipsychotic medications. One study[90] reported higher mortality rates with use of conventional and atypical antipsychotic medications compared with use of other psychotropic medications.

Nonelderly Adults. Death, stroke, and other cardiovascular symptoms have rarely been assessed in nonelderly adults taking atypical antipsychotic medications. One large cohort study[95] of patients aged 30 to 74 years reported higher rates of sudden cardiac death in those who had taken any antipsychotic medication (either conventional or atypical) compared with patients with nonuse. Differences between conventional and atypical antipsychotic medications were not statistically significant. For both classes of antipsychotic medications, risk increased with dose. Another cohort study of patients aged 16 to 85 years found that users of antipsychotic medications (either conventional or atypical) had greater odds of venous thromboembolism after adjusting for comorbidity and concomitant drug exposure.[96] Weight gain, fatigue, sedation, akathisia, and extrapyramidal symptoms are adverse effects of these drugs. Therefore, we focused on these outcomes in our meta-analyses of 85 trials (Table 2).

We found statistically significant associations with aripiprazole, quetiapine, risperidone, and olanzapine and weight gain. Olanzapine was particularly associated with weight gain (pooled OR, 11.3 [95% CI, 8.22-15.74]; NNH=3). Only 1 trial of olanzapine reported outcomes for diabetes. While the OR was 5.14 (95% CI, 0.57-244.28), this was not statistically significant. Two studies of ziprasidone found no association with weight gain. Sedation was associated with every atypical antipsychotic medication. Most atypical antipsychotic medications (except risperidone) were associated with fatigue. Only aripiprazole was associated with akathisia (pooled OR from 5 studies, 11.80; 95% CI, 7.40-19.61). Aripiprazole, quetiapine, and ziprasidone were associated with extrapyramidal symptoms.

Comparative Harms. We identified 1 head-to-head trial comparing olanza-

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pine with ziprasidone and 2 head-to-head trials comparing quetiapine with risperidone. Olanzapine was associated with an increased odds of weight gain (OR, 4.02; 95% CI, 2.25-7.48) compared with ziprasidone.[97] Compared with risperidone, quetiapine was associated with a higher odds of decreased salivation, neurological events, sedation, and agitation.

COMMENT

This systematic review demonstrates evidence for the efficacy of atypical antipsychotic medications for only a few of the off-label conditions that are currently being treated. First, aripiprazole, olanzapine, and risperidone are associated with small but statistically significant benefits for the treatment of behavioral symptoms in dementia. Drug doses vary, but are generally about 50% lower than those used in treating younger adults with schizophrenia or bipolar disorder. Second, 3 large trials of quetiapine demonstrated a significant benefit for treatment of generalized anxiety disorder. Third, risperidone is associated with significant improvement in OCD. Evidence did not support using atypical antipsychotic medications for substance abuse or eating disorders. We found only an inconclusive pilot trial regarding insomnia. The use of atypical antipsychotic medications for any of these conditions cannot be justified as evidence-based. This systematic review also identified some clinically important differences regarding potential benefits and adverse events between the atypical antipsychotic medications for off-label uses.

The use of atypical antipsychotic medications is associated with adverse outcomes, including a small but statistically significant increased risk of death in elderly patients with demen-

Table 1. Adverse Events Associated With Use of Atypical Antipsychotic Medications Compared With Placebo in Elderly Patients With Dementia

		Placebo		Atypical Antipsychotic Drugs		
	No. of Studies	No. of Adverse Events	Sample Size	No. of Adverse Events	Sample Size	Pooled OR (95% CI)
Cardiovascular event[a]						
Aripiprazole	1	12	121	42	366	1.20 (0.58-2.55)
Olanzapine	5	9	440	40	778	2.30 (1.08-5.61)
Quetiapine	3	15	254	29	355	1.10 (0.53-2.30)
Risperidone	6	34	1010	119	1757	2.10 (1.38-3.22)
Cerebrovascular accident						
Aripiprazole	3	2	253	2	340	0.70 (0.05-10.48)
Olanzapine	2	4	232	6	278	1.50 (0.33-7.44)
Quetiapine	2	6	241	3	185	0.70 (0.10-3.08)
Risperidone	4	8	753	24	1099	3.12 (1.32-8.21)
Increased appetite or weight increase						
Aripiprazole	2	10	223	23	472	1.00 (0.44-2.49)
Olanzapine	3	6	326	34	482	4.70 (1.87-14.14)
Quetiapine	1	4	142	5	94	1.90 (0.40-10.01)
Risperidone	2	5	236	14	281	3.40 (1.08-12.75)
Anticholinergic events						
Olanzapine	1	12	90	60	178	3.30 (1.62-7.17)
Sedation						
Aripiprazole	4	22	374	116	706	2.60 (1.57-4.54)
Olanzapine	5	25	440	158	778	4.60 (2.87-7.55)
Quetiapine	4	18	353	84	446	5.20 (2.93-9.51)
Risperidone	6	102	922	265	1260	2.30 (1.79-3.05)
Extrapyramidal symptoms						
Aripiprazole	4	16	374	39	706	1.30 (0.68-2.57)
Olanzapine	1	2	142	18	100	15.20 (3.50-138.55)
Quetiapine	3	9	254	18	355	1.20 (0.46-3.08)
Risperidone	5	31	916	130	1561	3.00 (1.96-4.70)
Urinary tract symptoms						
Aripiprazole	3	44	348	115	603	1.40 (0.92-2.09)
Olanzapine	1	1	94	19	204	9.50 (1.47-401.07)
Quetiapine	2	12	191	44	332	2.40 (1.16-5.15)
Risperidone	4	71	665	164	1060	1.60 (1.13-2.13)

Abbreviation: OR, odds ratio.
[a] Category excludes patients who experienced cerebrovascular accident.

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tia. Other cardiovascular symptoms, sedation, fatigue, extrapyramidal symptoms, and urinary tract symptoms are also associated with some or all of the studied atypical antipsychotic medications, with the latter 2 occurring in up to 8% and 18% of elderly patients, respectively. Concern for these adverse effects may have contributed to recent declines in atypical antipsychotic medication use in patients with dementia.[98] In nonelderly adults, fatigue and sedation are common. Akathisia is associated with aripiprazole use, and weight gain is common with several drugs, particularly olanzapine, in which more than 40% of patients may report increased appetite or weight gain. An individual patient's specific target symptoms, the effectiveness of other interventions, the value of modest symptomatic improvement, the individual's particular susceptibility and consequences of adverse events, and the goals of care should be considered in the antipsychotic medication treatment decision.

There are several distinct conclusions between this review and our prior review in 2006. Most notably, the use of any atypical antipsychotic medication for major depressive disorder was considered inconclusive in 2006. Numerous new trials have been sufficient to gain FDA approval for quetiapine and aripiprazole as augmentation therapy in major depressive disorder. A second change is the new evidence regarding the benefit of quetiapine for treating generalized anxiety disorder. Other clinically significant differences include: (1) the strength of evidence has increased from moderate to high for the efficacy of atypical antipsychotic medications in treating behavioral symptoms in patients with dementia, (2) the strength of evidence has decreased from moderate to low for quetiapine in pa-

Table 2. Adverse Events Associated With Off-Label Use of Atypical Antipsychotic Medications Compared With Placebo in Nonelderly Adults

		Placebo		Atypical Antipsychotic Drugs		
	No. of Studies	No. of Adverse Events	Sample Size	No. of Adverse Events	Sample Size	Pooled OR (95% CI)
Increased appetite or weight						
Aripiprazole	4	8	686	35	701	4.20 (1.88-10.56)
Olanzapine	11	103	819	382	818	11.30 (8.22-15.74)
Quetiapine	13	90	1846	279	2887	2.70 (2.07-3.58)
Risperidone	4	5	197	24	237	3.80 (1.35-13.09)
Ziprasidone	2	2	113	5	251	1.20 (0.19-13.59)
Diabetes						
Olanzapine	1	1	377	5	370	5.14 (0.57-244.28)
Quetiapine	6	11	1073	32	1753	1.50 (0.71-3.28)
Sedation						
Aripiprazole	7	73	810	160	820	3.00 (2.15-4.32)
Olanzapine	14	127	904	279	901	3.00 (2.29-3.82)
Quetiapine	18	373	2285	1668	3531	5.50 (4.78-6.43)
Risperidone	8	25	290	54	336	2.40 (1.39-4.34)
Ziprasidone	5	21	212	95	392	3.90 (2.15-7.44)
Fatigue						
Aripiprazole	4	31	686	82	701	2.90 (1.83-4.55)
Olanzapine	7	43	737	80	720	2.10 (1.37-3.12)
Quetiapine	13	74	2010	289	3072	2.90 (2.20-3.97)
Risperidone	4	9	233	9	274	0.80 (0.28-2.41)
Ziprasidone	2	0	69	8	111	Undefined (1.59-undefined)[a]
Akathisia						
Aripiprazole	5	24	769	190	779	11.80 (7.40-19.61)
Olanzapine	1	7	25	9	23	2.00 (0.50-8.92)
Quetiapine	4	5	488	10	632	1.30 (0.38-5.07)
Risperidone	1	0	18	1	19	Undefined (0.02-undefined)[a]
Ziprasidone	3	9	161	36	321	2.10 (0.96-5.15)
Extrapyramidal symptoms						
Aripiprazole	5	43	605	99	610	2.80 (1.83-4.19)
Olanzapine	3	18	65	17	71	0.90 (0.25-2.97)
Quetiapine	7	35	1100	87	1466	2.60 (1.72-4.06)
Risperidone	1	1	10	0	15	0 (0-26)
Ziprasidone	3	6	161	28	321	3.10 (1.15-10.62)

Abbreviation: OR, odds ratio.
[a] Undefined indicates values that were incalculable because the number of events was zero in 1 of the 2 study groups.

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tients with OCD, and (3) new evidence has emerged that atypical antipsychotic medications are ineffective for eating disorders and substance abuse disorder.

There are several limitations to our findings. First, unidentified, unpublished, or excluded studies might have reported results different from those included here. Second, studies published after June 1, 2011, including a recent large randomized controlled trial[99] of risperidone therapy for patients with military-related PTSD and symptoms resistant to SSRIs, were not included in our review. Third, we detected unexplained heterogeneity, which may indicate the presence of publication bias, in our pooled results for OCD. This finding accordingly tempers our conclusion about OCD. Fourth, our meta-analysis, particularly for dementia, distills broad heterogeneities across patient and treatment circumstances, and the studies used variable definitions and measures of agitation, which complicates the clinical interpretation and application of the findings. Even so, the evidence is reasonably consistent regarding a small improvement, on average, in clinically relevant symptoms for patients with dementia. Fifth, we did not compare atypical antipsychotic medications to nonpharmacological therapy. Sixth, we found no studies on off-label use for the 3 newer atypical antipsychotic medications (asenapine, iloperidone, or paliperidone). Lastly, most studies were sponsored by drug manufacturers (for example, 27 of 38 dementia trials and 12 of 14 anxiety trials). The existence of the CATIE-AD study, which was federally sponsored and reported results consistent with the industry-sponsored studies, increases our confidence in the conclusions regarding atypical antipsychotic medications for elderly patients with dementia.

In summary, we identified a large amount of literature on the off-label uses of atypical antipsychotic medications. The benefits and harms vary among atypical antipsychotic medications for off-label use. For symptoms of psychosis, agitation, and global behavioral symptoms in elderly patients with dementia, small but statistically significant benefits were observed for risperidone, aripiprazole, and olanzapine. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder, and risperidone was associated with benefits in the treatment of OCD. Importantly, adverse effects of atypical antipsychotic medications are common. This evidence should prove useful for clinicians considering off-label prescribing of atypical antipsychotic medications, and should contribute to optimal treatment decision making for individual patients with specific clinical symptoms and unique risk profiles.

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