Efficacy and Adverse Effects of Atypical Antipsychotics for Dementia: Meta-analysis of Randomized, Placebo-Controlled Trials

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Objective: *Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease (AD) and other dementia. Several clinical trials have not shown efficacy, and there have been concerns about adverse events. The objective of this study was to assess the evidence for efficacy and adverse events of atypicals for people with dementia* **Methods:** *MEDLINE, the Cochrane Register of Controlled Trials, meetings, presentations, and information obtained from sponsors were used in this study. Published and unpublished randomized, placebo-controlled, double-blind, parallel-group trials in patients with AD or dementia of atypical antipsychotics marketed in the United States were studied. Clinical and trials characteristics, outcomes, and adverse events were extracted. Data were checked by a second reviewer. Fifteen trials including 16 contrasts of atypical antipsychotics with placebo met selection criteria: aripiprazole (k = 3), olanzapine (k = 5), quetiapine (k = 3), and risperidone (k = 5). A total of 3,353 patients were randomized to drug and 1,757 to placebo. Standard meta-analysis methods were used to summarize outcomes.* **Results:** *Quality of the reporting of trials varied. Efficacy on rating scales was observed by meta-analysis for aripiprazole and risperidone, but not for olanzapine. Response rates were frequently not reported. There were smaller effects for less severe dementia, outpatients, and patients selected for psychosis. Approximately one-third dropped out without overall differences between drug and placebo. Adverse events were mainly somnolence and urinary tract infection or incontinence across drugs, and extrapyramidal symptoms or abnormal gait with risperidone or olanzapine. Cognitive test scores worsened with drugs. There was no evidence for increased injury, falls, or syncope. There was a significant risk for cerebrovascular events, especially with risperidone; increased risk for death overall was reported elsewhere.* **Conclusions:** *Small statistical effect sizes on symptom rating scales support the evidence for the efficacy of aripiprazole and risperidone. Incomplete reporting restricts estimates of response rates and clinical significance. Dropouts and adverse events further limit effectiveness. Atypicals should be considered within the context of medical need and the efficacy and safety of alternatives. Individual patient meta-analyses are needed to better assess clinical significance and effectiveness.* (Am J Geriatr Psychiatry 2006; 14:191–210)

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Atypical antipsychotic medications, with or without psychosocial and environmental interventions, are frequently used to treat delusions, hallucinations, aggression, and agitation that occur in a majority of elderly patients with dementia during their illness courses, and have been the mainstay of psychopharmacologic treatment for this purpose during the last several decades. Their overuse in the 1980s led to federal regulations requiring their oversight in U.S. nursing homes (42 CFR part 483).

The atypical antipsychotics (i.e., risperidone, olanzapine, quetiapine, and aripiprazole, in order of introduction) generally have replaced conventional antipsychotics (e.g., haloperidol and thioridazine) and have been considered preferred pharmacologic treatments for behavioral disturbances associated with dementia[1,2] in part because of clinical trials evidence[3–9] perceived safety advantages compared with other medications and expert clinical opinion.[1,2] There is little clinical trials evidence for the efficacy of other classes of psychotropic medication such as benzodiazepines, anticonvulsants, and antidepressants for treating these behavioral signs and symptoms.[10]

The perceived safety advantages of atypicals compared with conventionals or other medication include less sedation, cardiovascular adverse effects, postural instability, falls, and movement disorders, although the few direct comparison trials are inadequate to address this.[4,11,12] Moreover, both conventional antipsychotic use and the presence of psychosis have been associated with more rapid cognitive decline in patients with dementia (see the additional bibliography online).

Concern has been raised recently about increased risk for cerebrovascular adverse events (CVAEs, e.g., stroke and transient ischemic episodes), metabolic syndrome, and other adverse events that may be caused by certain atypicals (for references, see [13] and additional bibliography online). Heath Canada issued an advisory in late 2002[14] and the U.S. Food and Drug Administration (FDA) added warnings of increased CVAEs to the U.S.-prescribing information for risperidone in April 2003, olanzapine in January 2004, and aripiprazole in February 2005 (www.risperdal.com, www.zyprexa.com, www.abilify.com, accessed March 31, 2005). There is limited access to this data because most of the trials have not been published and CVAEs were generally not reported.

On April 11, 2005, the FDA issued a health advisory for increased risk for death with atypicals in people with dementia but did not provide data (http://www.fda.gov/cder/drug/advisory/antipsychotics.htm). Independently, we performed a meta-analysis of all available data and reported increased risk for death with antipsychotics of odds ratio: 1.54, (95% confidence interval [CI]: 1.06–2.23; $Z = 2.28$, $p = 0.02$) consistent with the FDA's assessment.[13]

In light of the expanding evidence base and the controversies surrounding their use, we conducted independent, individual study-based meta-analyses of atypical antipsychotics trials to assess the evidence for efficacy and adverse events with their use in patients with dementia, compare benefits with risks, and identify current issues. Previous systematic reviews or meta-analyses have been incomplete in this regard (see the additional bibliography online).

METHODS

Search Strategy, Trials Selection, and Data Retrieval

The search strategy was described in detail previously.[13] Briefly, MEDLINE (1966–April 2005) and the Cochrane Central Register of Controlled Trials (2005, Issue 1)[15] were searched using the headings aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone (i.e., atypical antipsychotics marketed in the United States), dementia, "Alzheimer disease," and "clinical trial." This was supplemented by hand reviewing materials from conferences and web postings. Pharmaceutical manufacturers were queried and information was requested as needed.

Trials were included if they met the following criteria: 1) parallel group, double-blinded, placebo-controlled with random assignment to an orally administered atypical antipsychotic or placebo; 2) patients had Alzheimer disease, vascular dementia, mixed dementia, or a primary dementia; and 3) numbers of patients randomized and at least one outcome measure or adverse event was obtainable. Reports did not need to be published or peer-reviewed and could have been reported in various formats. (Some sources presented incomplete information and addi-

tional information was obtained though other data presentations or from the trials' sponsors.)

Information extracted included design characteristics, selection criteria (dementia diagnoses and presence of psychosis of dementia[16]), medication doses, locations, trials durations, age, gender, baseline cognitive scores, numbers randomized, clinical outcomes on rating scales, dropouts, and adverse events after randomization. Outcomes and adverse events data were from the intent-to-treat or last-observation-carried-forward samples. Data were abstracted by one and checked by another investigator and discrepancies resolved. In addition, we extracted total drug and placebo exposure duration (i.e., patient-years of treatment) from various sources.[8,13,17–19]

Statistical Analyses

The outcomes and the numbers randomized into each drug and placebo for each trial were statistically combined using the DerSimonian and Laird random-effects model for dropouts and adverse events, the Mantel-Haenszel fixed-effect model for dichotomous clinical outcomes, and inverse variance methods for continuous and ordinal clinical outcomes. Effects were expressed as odds ratios (ORs) and absolute rate differences (RDs) with their 95% confidence intervals (CIs) and p values, and as weighted mean differences (WMD) and standardized mean differences (SMD) using Review Manager Version 4.2 software[20] (SMDs were used when effects from different outcome instruments were combined and to express effect sizes in standard deviation units.). Because there were few dose-ranging trials, sparse outcomes for adverse events, and to avoid multiple comparisons with the same placebo group, we combined dosage groups within each trial to make one contrast with placebo. The possibility of a dose response within dose-ranging trials was explored descriptively if there was a significant overall effect by meta-analysis of the particular drug.

χ^2 tests and the I^2 statistic derived from the χ^2 values were used to test heterogeneity among the contrasts. I^2 approximates the proportion of total variation in the effect size estimates that is the result of heterogeneity rather than sampling error. An α error $p \leq 0.20$ and $I^2 \geq 50\%$ were taken as indicators of heterogeneity of outcomes.

Funnel plots in which the SMD of the main outcome of each trial was plotted against the standard errors of the SMDs were used to evaluate potential retrieval bias and to compare the published trials with the nonpublished.

We compared the following by stratification as subgroup or sensitivity analyses for efficacy and adverse events: whether or not sample selection required that patients had to have psychotic symptoms or psychosis of dementia,[16] outpatient versus nursing home status, cognitive severity (i.e., mean baseline Mini-Mental State Examination [MMSE] score per trial >10 or not), or by drug used. Potential differences between two or more subgroups were investigated by subtracting the sum of the heterogeneity χ^2 statistics of the subgroups from the overall χ^2 statistic and comparing the result with a χ^2 distribution with one less degree of freedom than the number of subgroups. (For references to statistical methods, see the additional bibliography online.)

RESULTS

Search Flow

The retrieval results are detailed elsewhere[13] and ultimately yielded five trials from MEDLINE and six from the Cochrane registry that included the five MEDLINE references. One placebo-controlled trial of olanzapine (N = 16 subjects)[21] was not included because the only available documentation was an abstract with inadequate information; one was a review with information on an olanzapine trial not contained elsewhere.[22]

One recently published trial of quetiapine was included but was not identified in the literature search because it had not been published when the search was performed.[8] Another very recently published report of an olanzapine trial, already included in the analysis based on other material, was identified during the final stages of the manuscript preparation[9] and included additional information that was added to the analyses. Thirteen posters and slide presentations from medical conferences were obtained containing information on 10 trials.

Altogether, 18 placebo-controlled, randomized, clinical trials were identified. Three risperidone trials were not included because of unavailability of data,

including one 4-week-long nursing home trial in Belgium (RIS-BEL-14, N = 39 subjects), one 12-week-long multicenter nursing home trial terminated early (RIS-INT-83, N = 18), and one 12-week-long outpatient trial in Germany using heterogeneous, not necessarily demented patients with "organic psychosis syndrome" (RIS-GER-16, N = 815).

Trials and Subject Characteristics

Fifteen trials fulfilled the search criteria and were included in the review (Table 1). They were three aripiprazole trials, two in nursing homes and one in outpatients (10-week durations); five olanzapine trials, two in nursing homes and three in outpatients, and one with a risperidone comparison (6–26-week durations); five risperidone trials, including the outpatient trial with an olanzapine comparison, four in nursing homes and one with an haloperidol comparison (8–12-week durations); and three quetiapine nursing homes trials, one with a haloperidol comparison and another with rivastigmine (10–26-week durations). Thus, 11 trials were performed in nursing homes and four with outpatients. Eight trials allowed dosage adjustment; two were fixed-dose and five dose-ranging trials with two to four fixed doses of study drug.

Overall, 3,353 patients were randomized to drug and 1,757 to placebo. We counted 603 randomized to aripiprazole, 1,184 to olanzapine, 391 to quetiapine, and 1,175 to risperidone. In two trials, 293 were randomized to haloperidol. Nine trials allowed only patients with AD to be included and comprised 53% of the subjects. Six allowed subjects to have various dementia diagnoses, including mainly AD, vascular and mixed dementia, and comprised 73% with AD. Overall, 87% of all subjects had AD. Seven trials specifically required psychosis of AD; two required dementia with psychosis; five allowed dementia with agitation or aggression and did not preclude hallucinations or delusions; and one required AD with agitation. The weighted mean age per trial was 81.2 years (standard deviation [SD]: 7.8) and 70% were female. The extent of cognitive impairment ranged from mild to severe with 13 trials having mean MMSE scores of 11.3, range of means per trial, 5.4–21.5, on a 30-point scale.

Trials Publication Bias

A funnel plot did not show evidence of selection bias with symmetry around the mean overall effect (plot not shown). Also, there was no difference between published (k = 8) and unpublished (k = 6) trials on a selected efficacy rating from each trial, SMD of −0.15 (95% CI: −0.28–−0.02; Z = 2.18, p = 0.03) versus −0.16 (95% CI: −0.26–−0.06; Z = 3.29, p = 0.001), respectively (olanzapine trial HGIC was not included).

Meta-analyses of Dropouts

We reported previously[13] that there was no significant difference in all-cause dropouts by meta-analysis (OR: 1.07, 95% CI: 0.88–1.30, Z = 0.68, p = 0.50), 32.2% of the drug-treated versus 32.4% of the placebo-treated patients, but with significant heterogeneity among the trials ($\chi^2 = 30.89$, df = 15, $I^2 = 51.4\%$, p = 0.009). There were statistical trends by meta-analysis for more olanzapine-treated patients and fewer aripiprazole-treated patients compared with placebo to dropout (OR: 1.34, 95% CI: 0.92–1.96; Z = 1.51, p = 0.13 and OR: 0.71, 95% CI: 0.52–0.96; Z = 2.23, p = 0.03, respectively) and appear to have contributed to the heterogeneity of the effect.

Quality of the Trials

All trials were randomized, double-blind with medications generally reported as identically appearing with placebo. Methods of randomization or of blinding medications were generally not reported. There was no evidence of attrition bias in that there was no difference in dropouts overall between drug and placebo subjects. There was inconsistency, variability, and selectivity in reporting of methods and results. Primary outcomes and methods of analyses also were often not explicitly stated or reported; secondary outcomes were variously reported (see subsequently).

Efficacy

Efficacy outcomes are listed in Table 1. Not all outcomes were reported in enough trials or with enough detail to abstract or estimate effect sizes. Generally, trials of specific drugs used different outcomes from trials of other drugs. The Behavioral

TABLE 1. Descriptions of Placebo-Controlled Trials Included in the Meta-analyses

Reference/Study Code	Key Inclusion Criteria	Location	Length (weeks)	Dose	Size (N)	Protocol Outcomes
Aripiprazole						
Breder et al., 2004 (p)[31]/CN 138-004	AD with psychosis	NH	10	2, 5, and 10 mg/d groups	487	BPRS, **NPI**, CMAI, CGI-S, CGI-I
Streim et al., 2004 (p)[32](p),[33](p),(p)[34]/CN 138-005	AD with psychosis	NH	10	2–15 mg/d mean: 8.6 mg/d	256	BPRS, **NPI**, CMAI, **CGI-S**, CGI-I, CSDD
DeDeyn et al., 2003 (p)[35](p),[33](p),[34]/CN 138-006	AD with psychosis	Outpt	10	2–15 mg/d, mean: 10 mg/d	208	BPRS, **NPI**, CGI-S, CGI-I
Olanzapine						
Satterlee et al., 1995 (abstract),[22] (review),[36] (chapter),[37] (p)[38]/HGAO	AD with psychosis	Outpt	8	1–8 mg/d, modal dose: 2.4 mg/d	238	BEHAVE-AD, CGI-S
Street et al., 2000[5](p),[38]/HGEU	AD with agitation, delusions, or hallucinations	NH	6	5, 10, and 15 mg/d groups	206	BPRS, **NPI**
Deberdt et al., 2004[9](p),[39](p),[40](p)[38]/HGGU	Dementia with hallucinations or delusions (78% AD, 5% VaD, 17% mixed)	Outpt	10	2.5–10 mg/d, mean: 5.2 mg/d; and risperidone 0.5–2 mg/d, mean: 1.0 mg/d	494	BPRS, **NPI**, CMAI, **CGI-S**, PDS, CSDD
Kennedy et al., 2004 (p)[41](p),[38]/HGIC	AD, nonpsychotic, nonagitated, nondepressed, MMSE 14–26	Outpt	26	5 mg/d	268	ADASc, CIBIC+
DeDeyn et al., 2004[7] (p),[38]/HGIV	AD with delusions or hallucinations	NH	10	1, 2.5, 5, and 7.5 mg/d dose groups	652	BPRS, **NPI**, **CGI-C**
Quetiapine						
Ballard et al., 2005[8]	AD with agitation	NH	26	50–100 mg/d; rivastigmine 6–12 mg/d	80	**CMAI,** SIB
Tariot et al., 2002 (p)[12]/5077 US-039	Elderly patients with psychosis (75% AD, 15% VaD, 10% other diagnoses)	NH	10	25–600 mg, median: 97 mg/d; haloperidol 0.5–12 mg/d, median: 1.9 mg/d	378	**BPRS**, NPI**, CGI-S,** CGI-C MOSES, PSMS
Zhong et al., 2004 (p)[42]/5077 US-046	Dementia with agitation (73% AD, 7% VaD, 8% mixed)	NH	10	100 and 200 mg/d groups	333	**PANSS-EC**, CGI-C
Risperidone						
Brodaty et al., 2003[6]/RIS-AUS-05	Dementia with aggression, MMSE ≤23, (58% AD, 29% VaD, 13% mixed)	NH	12	0.50–2 mg/d, mean: 0.95 mg/d	345	BEHAVE-AD, **CMAI**, CGI-C, CGI-S, FAST
DeDeyn et al., 1999[4] (p),[43]/RIS-INT-24	Dementia, MMSE ≤23, BEHAVE-AD ≥8 (67% AD, 26% VaD, 7% mixed)	NH	12	0.50–4 mg/d, mean: 1.1 mg/d; haloperidol: 0.50–4 mg/d, mean: 1.2 mg/d	344	**BEHAVE-AD**, CMAI, CGI-S
Katz et al., 1999[3]/RIS-USA-63	Dementia, MMSE ≤23, BEHAVE-AD ≥8 (73% AD, 15% VaD, 12% mixed)	NH	12	0.5, 1, and 2 mg/d groups	625	**BEHAVE-AD**, CMAI, CGI-S
Mintzer et al., 2004 (p)[44]/RIS-USA-232	AD with psychosis, MMSE 5–23	NH	8	0.5–1.5 mg/d, mean: 1.0 mg/d	473	**BEHAVE-AD**, CGI-C

Note: Bold indicates protocol-specified primary outcomes.

(p): Poster presentation at medical meeting' AD: Alzheimer disease; VaD: vascular dementia; NH: nursing home; N: number randomized; MMSE: Mini-Mental State Examination; BPRS: Brief Psychiatric Rating Scale; NPI: Neuropsychiatric Inventory; PANSS-EC: Positive and Negative Symptoms Scale–Excitatory Component; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; CMAI: Cohen Mansfield Agitation Inventory; CGI-C: Clinical Global Impression–Change; CGI-I: Clinical Global Impression–Improvement; CGI-S: Clinical Global Impression–Severity; CIBIC+: Clinician's Interview Based Impression of Change plus Caregiver Input; SIB: Severe Impairment Battery; CSDD: Cornell Scale for Depression in Dementia; MOSES: Multidimensional Observation Scale for Elderly Subjects; FAST: Functional Assessment Staging Test; PDS: Progressive Deterioration Scale; PSMS: Physical Self Maintenance Scale.

Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[23] and Cohen-Mansfield Agitation Inventory (CMAI)[24] were generally used for risperidone trials, and the Brief Psychiatric Rating Scale (BPRS)[25] and Neuropsychiatric Inventory (NPI)[26] for aripiprazole and some olanzapine trials. Table 2 lists the baseline scores on these outcomes by individual trial as available. The Clinical Global Impression–Change (CGI-C), CGI-Severity (CGI-S), or in several trials modified versions of the Alzheimer's Disease Cooperative Study–Clinician's Impression of Change (ADCS-CGIC)[27,28] were used as main clinical outcomes in all but two trials, yet they were generally not reported or inadequately reported. The NPI and CMAI are structured interviews with patients' caregivers.

Effect sizes and meta-analysis results by drug and by rating scales are displayed in Figure 1. The outcomes based on definitions of responders, usually dichotomization of the continuous or ordinal scales, are displayed in Figure 2.

Aripiprazole. The three aripiprazole trials retrieved were designed similarly, with similar selection criteria, AD with psychosis, 10-week treatment durations, and the same primary and secondary outcomes, i.e., BPRS, NPI, CGI-S, the CMAI in two and the Cornell Scale for Depression in Dementia[29] in one. Two were nursing home trials and one trial, CN 138–006, was an outpatient trial.

Significant effects by meta-analysis were observed on the BPRS and NPI change scores (WMD = −2.49, 95% CI:−4.05–−0.94, p = 0.002 and WMD = −3.63, 95% CI: −6.57–−0.69, p = 0.02, respectively). A significant effect by meta-analysis on the CMAI was observed but was based on only the two nursing home trials (WMD = −4.05, 95% CI: −6.58–−1.52, p = 0.002).

Global clinical ratings were reported only as continuous outcomes with a one- to seven-point range and not as categorical or individual response-based outcomes. The CGI-S was significant in favor of aripiprazole by meta-analysis (WMD = −0.15, 95% CI: −0.29–0.00, p = 0.05). The effect on the CGI-I (WMD = −0.18, 95% CI: −0.39–0.03, p = 0.09) was nonsignificant but effect sizes were estimated using the reported p values in the absence of information on the standard deviations.

There were overall significant effects on NPI total and on NPI psychosis subscale "responses," each defined as a ≥50% improvement on the baseline score, OR of 1.50 (95% CI: 1.14–1.99, p = 0.005) and OR of 1.38 (95% CI: 1.04–1.83, p = 0.02), respectively. Pooled "responses" were 48% aripiprazole and 38% placebo, and 61% versus 54% for NPI total and NPI psychosis subscale, respectively.

Olanzapine. Of the five trials identified, one 8-week long outpatient trial, HGAO, did not provide quantitative information on outcomes, including the BEHAVE-AD and a global rating, but described them as nonsignificant. One 6-month-long outpatient trial, HGIC, selected nonpsychotic, nonagitated, nondepressed mildly to moderately cognitively impaired patients with AD and was intended to assess whether olanzapine would improve cognition, not whether it might improve behavioral symptoms. These trials were included in adverse event analyses.

The remaining three trials included two nursing home trials of patients with AD, one with a 6-week treatment period requiring subjects with agitation, delusions, or hallucinations and the other 10 weeks requiring patients with delusions or hallucinations. Both used fixed dosing ranges. The third placebo-controlled trial, HGGU, was with outpatients treated over 10 weeks, selecting patients with dementia with hallucinations or delusions, and comparing flexible doses of olanzapine with doses of risperidone. Among these three trials, there were nonsignificant effects by meta-analysis on the BPRS and NPI (WMD of −0.92, 95% CI: −2.48–0.63, p = 0.24 and of −1.74, 95% CI: −4.68–1.20, p = 0.25, respectively).

None of the trials provided an assessment of categorical treatment response using the global scales included in the protocols. A CGI-C was reported in one nursing home trial, HGIV, as a continuous measure (WMD = −0.25, 95% CI: −0.52–0.02, p = 0.07). One trial, HGEU, provided treatment response on the basis of a ≥50% improvement on an NPI core score, comprising the hallucinations and delusions of the psychosis subscale and the agitation item (OR: 2.28, 95% CI: 1.16–4.50, p = 0.02), 54% versus 34%. Another trial, HGGU, provided response on the basis of a ≥30% improvement on the NPI psychosis subscale (OR: 0.83, 95% CI: 0.50–1.39, p = 0.49), 62% versus 66%.

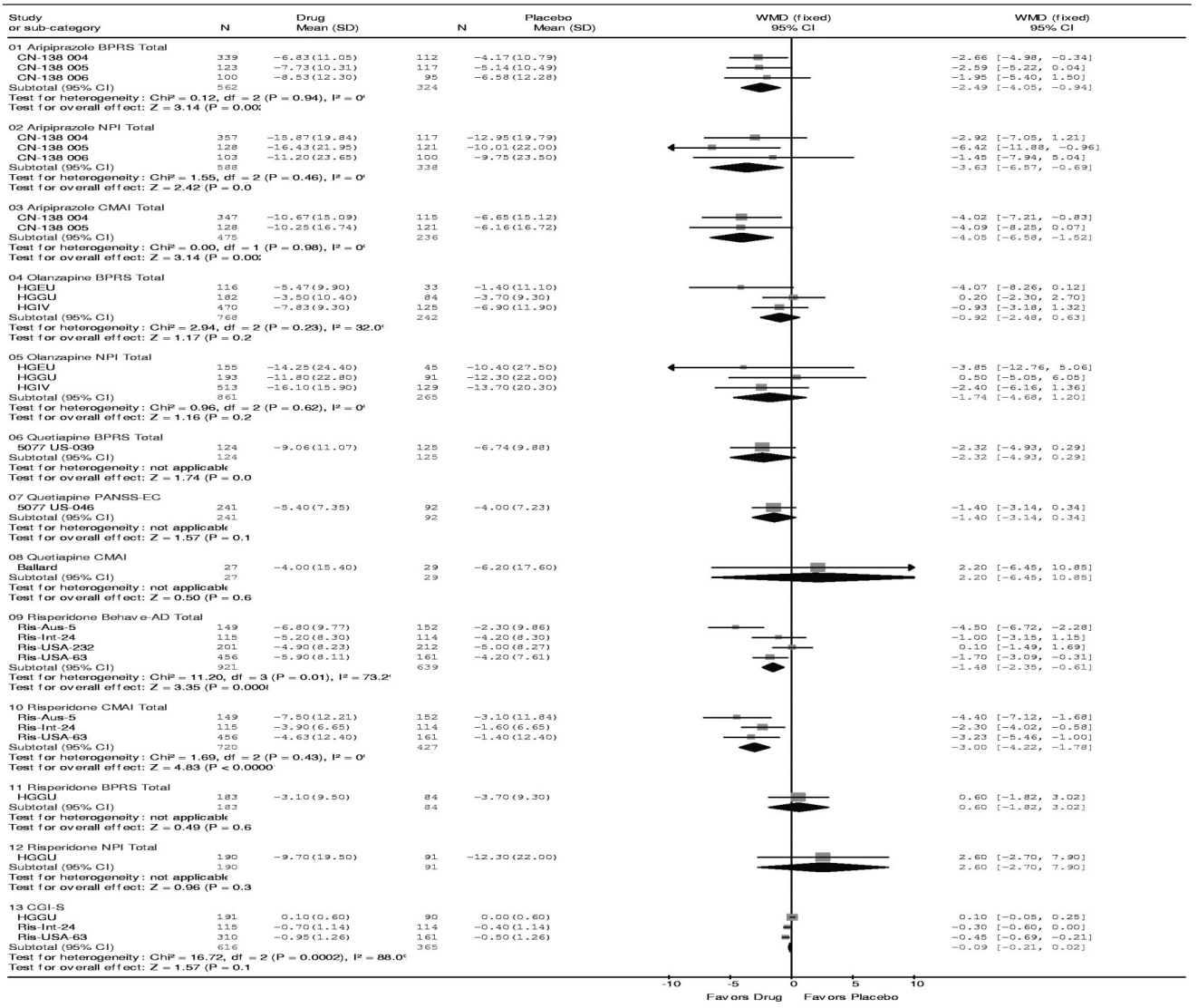
Quetiapine. The designs, selection criteria, and outcomes scales differed substantially among the three quetiapine trials and did not allow for the combining of efficacy outcomes (Table 1). Trial 5077

TABLE 2. Characteristics and Baseline Rating Scale Scores of Patients Included in the Meta-analyses

Reference/Study Code	Key Clinical Characteristics/Location	Size, N	Age Range, years, (SD)	Gender (% female)	MMSE (SD)	BPRS (SD)[a]	BEHAVE-AD (SD)	NPI (SD)	CMAI (SD)
Aripiprazole									
Breder et al., 2004 (p)[31]/CN 138-004	AD with psychosis/NH	487	82.5 56–97	79	12.4 (4.4)	28.4 (10.6)		41.4 (19.6)	56.5 (17.8)
Streim et al., 2004 (p)[32](p)[33](p),[34]/CN 138-005	AD with psychosis/NH	256	83 59–96	76	12.9 (4.3)[c]	27.6 (11.1)		37.8 (18.7)	57.4 (18.6)
DeDeyn et al., 2003 (p)[35](p),[33](p),[34]/CN 138-006	AD with psychosis/Outpt	208	81.5 (6.5) 56–99	72	13.6 (4.3)[c]	25.5 (12.8)		40.0 (18.8)	
Olanzapine									
Satterlee et al., 1995 (abstract)[22] (review), 36 (chapter),[37] (p),[38]/HGAO	AD with psychosis/Outpt	238	78.6 64–94	66	Not reported		Not reported		
Street et al., 2000[5] (p),[38]HGEU	AD with agitation, delusions, or hallucinations/NH	206	82.8 (6.6) 61–97	61	6.7 (6.4)	28.3 (10.7)		42.4 (22.5)	
Deberdt et al., 2004[9] (p),[39](p),[40](p),[38]/HGGU	Dementia with hallucinations or delusions/Outpt	494	78.4 (7.4)	66	14.5 (5.6)	21.1 (10.9)		42.2 (20.1)[b]	14.3 (4.8)[d]
Kennedy et al., 2004 (p)[41](p),[38]/HGIC	AD, nonpsychotic, nonagitated, nondepressed, MMSE 14–26/Outpt	268	78 (8.0)	56	21.5 (3.6)				
DeDeyn et al., 2004[7] (p),[38]/HGIV	AD with delusions or hallucinations/NH	652	76.6 (10.4)	75	13.7 (5.1)	26.6 (12.0)		33.9 (18.8)	
Quetiapine									
Ballard et al., 2005[8]	AD with agitation/NH	80	83.8 (7.7)	80	Not reported				58.8 (17.7)
Tariot et al., 2002 (p)[12]/5077 US-039	Elderly patients with psychosis (75% AD, 15% VaD, 10% other)/NH	378	83.9 (6.5) 66–99	73	12.8 (5.3)	21.5 (10.1)		Not reported	
Zhong et al., 2004 (p)[42]/5077 US-046	Dementia with agitation (73% AD, 7% VaD, 8% mixed)/NH	333	83.2 (7.5)	74	5.4 (4.0)				
Risperidone									
Brodaty et al., 2003[6]/RIS-AUS-05	Dementia with aggression, MMSE ≤23 (58% AD, 29% VaD, 13% mixed)/NH	345	82.7 (7.1)	71	5.5 (5.7)		18.8 (11.0)		33.5 (12.7)[d]
DeDeyn et al., 1999[4] (p),[43]/RIS-INT-24	Dementia, MMSE ≤23, BEHAVE-AD ≥8 (67% AD, 26% VaD, 7% mixed)/NH	344	81 56–97	56	8.4 (7.8)		16.5 (6.3)		26.6 (11.2)[d]
Katz et al., 1999[3]/RIS-USA-63	Dementia, MMSE ≤23, BEHAVE-AD ≥8 (73% AD, 15% VaD, 12% mixed)/NH	625	82.7 (7.7)	68	6.6 (6.3)		15.8		Not reported
Mintzer et al., 2004 (p)[44]/RIS-USA-232	AD with psychosis, MMSE 5–23/NH	473	83.3 (7.3)	77	13.2 (5.0)		16.3 (9.7)		

[a]: BPRS item scores for aripiprazole and quetiapine trials are scaled from 1–7, range of total score 18–126; for olanzapine items are scaled 0–6, range of total 0–108. Eighteen points were subtracted from the mean scores to compensate for different scaling.
[b]: NPI 10-item version.
[c]: Pooled SD for MMSE from trial CN 138-005, and trial CN 138-006.
[d]: CMAI aggression subscale.
(p): Poster presentation at medical meeting; AD: Alzheimer disease; VaD: vascular dementia; NH: nursing home; N: number randomized; MMSE: Mini-Mental State Examination; BPRS: Brief Psychiatric Rating Scale; NPI: Neuropsychiatric Inventory; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; CMAI: Cohen Mansfield Agitation Inventory.

FIGURE 1. Efficacy Outcomes by Individual Comparisons: Aripiprazole, Olanzapine, Quetiapine, and Risperidone Compared With Placebo (weighted mean differences).



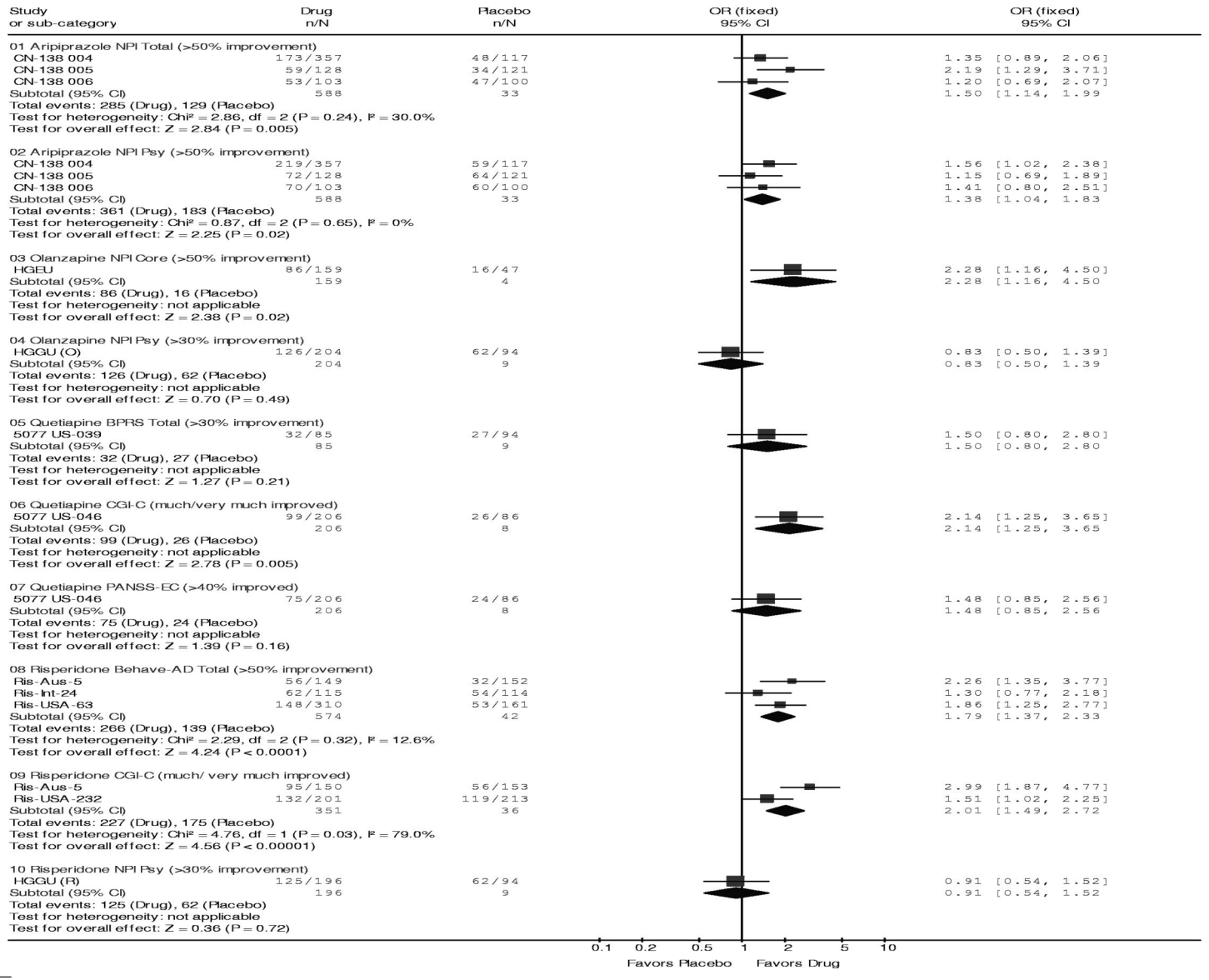
Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; WMD: weighted mean difference.

US-039 enrolled primarily nursing home patients with psychosis and separately assessed those with AD. Trial 5077 US-046 chose nursing home patients with a primary dementia, AD, vascular or mixed, mainly manifesting agitation severe enough to require an antipsychotic. A third, smaller trial chose nursing home patients with AD and agitation and compared quetiapine treatment with rivastigmine and placebo.

Trial 5077 US-039 showed no significant effect on the BPRS (WMD = −2.32, 95% CI: −4.93–0.29, p = 0.08). Trial 5077 US-046 showed no statistically significant effect for the 100-mg/d and 200-mg/d quetiapine treatment groups combined (WMD = −1.40, 95% CI: −3.14–0.34, p = 0.12) on the PANSS-EC, a measure of agitation, but a significant effect with the 200-mg/day dosage. There was no significant effect for quetiapine on the CMAI in the smaller trial.[8]

There was no significant response difference using

FIGURE 2. Dichotomized Efficacy Outcomes ("responders") by Scale by Drug by Comparison: Aripiprazole, Olanzapine, Quetiapine, and Risperidone (odds ratios)



Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; OR: odds ratio; n/N: number of events/total sample.

a change on the BPRS total of ≥30% as the definition of response in trial 5077 US-039 (OR: 1.50, 95% CI: 0.80–2.80, p = 0.21), 38% versus 29%, and using a change on the PANSS-EC of ≥40% in trial 5077 US-046 (OR: 1.48, 95% CI: 0.85–2.56, p = 0.16), 36% versus 28% (Figure 2). There was a significant CGI-C response in trial 5077 US-046 based on much or very much improved (OR: 2.14, 95% CI, 1.25–3.65, p = 0.005), 48% versus 30%, but no information on the CGI-C from trial 5077 US-039.

Risperidone. Three of the risperidone trials were similarly designed in that they selected nursing home patients with primary dementia who were agitated, had a minimum score on the BEHAVE-AD of ≥8, and were treated for 12 weeks. Trial RIS-AUS-05 selected patients particularly with aggression. The trials also used similar efficacy outcomes, i.e., the BEHAVE-AD, CMAI, and global ratings. A fourth trial, RIS-USA-232, selected ambulatory nursing home patients with AD and psychosis with an MMSE ≥5 who were treated for 8 weeks, resulting in patients with a mean MMSE of 13.2, generally twice as high as the mean MMSE in the other risperidone trials (Table 2). A fifth trial, HGGU, sponsored by the manufacturer of olanzapine, compared the two drugs as described here and also resulted in less cognitively impaired subjects, mean MMSE of 14.5, than the three nursing home trials. This trial did not share common outcomes with the other risperidone trials except for the CGI-S and CMAI.

Among the four trials using the BEHAVE-AD, there was overall significant improvement with risperidone (WMD = −1.48, 95% CI: −2.35–−0.61, p = 0.0008) and on the CMAI used in three trials (WMD = −3.00, 95% CI: −4.22–−1.78, p <0.00001) (Figure 1). There was no statistically significant effect overall by meta-analysis on the CGI-S as a continuous variable (WMD = −0.09, 95% CI: −0.21–0.02, p = 0.12), the BPRS and NPI in the outpatient trial HGGU with olanzapine.

Using an improvement on the BEHAVE-AD of ≥50% (or ≥30% for RIS-INT-24 because the ≥50% criterion was not available) as a definition of response, there was a significant effect by meta-analysis of three of the trials (OR: 1.79, 95% CI: 1.37–2.33, p <0.0001, 46% versus 33% pooled responders). A CGI-C as a categorical variable was available for two trials, RIS-AUS-5 and RIS-USA-232, showing overall significant effects (OR: 2.01, 95% CI: 1.49–2.72, p <0.00001, 65% versus 48% pooled responders). Notably, CGI-C responses could not be obtained for three trials, two of which showed nonsignificant results on their primary outcomes.

Effect on Psychosis Ratings

The effects with four of the drugs on specific psychosis subscales of the BPRS, NPI, or BEHAVE-AD are displayed in Figure 3. There were no significant effects by meta-analysis with three aripiprazole and three olanzapine trials on the BPRS and NPI psychosis subscales and with no single trial showing a significant effect. For aripiprazole, the BPRS and the NPI psychosis subscale scores by meta-analysis were WMD = −0.45 (95% CI: −1.04–0.14, p = 0.14) and WMD = −0.72 (95% CI: −1.53–0.09, p = 0.08), respectively. For olanzapine, the NPI psychosis subscale WMD was −0.37 (95% CI: −1.19–0.46, p = 0.38). For quetiapine, the NPI psychosis subscale WMD was −0.03 (95% CI: −1.52–1.46, p = 0.97).

There was a significant effect by meta-analysis with risperidone on the BEHAVE-AD psychosis subscale from three trials (WMD = −0.79, 95% CI: −1.20–−0.37, p = 0.0002), but a nonsignificant effect on the NPI psychosis subscale in the HGGU outpatient trial with a WMD of 0.50 (95% CI: −0.87–1.87, p = 0.47). Trial RIS-INT-24 did not report the BEHAVE-AD psychosis subscale.

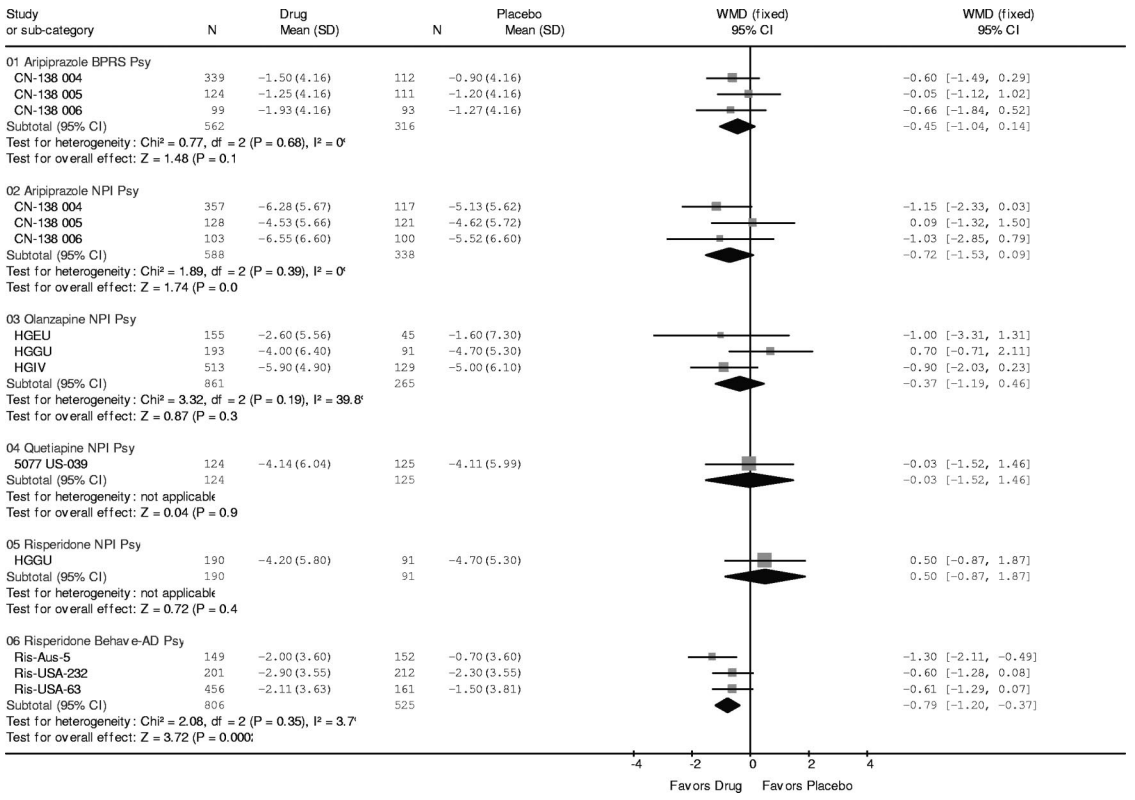
Only one of 14 contrasts was significant on a psychosis subscale rating; none of the six available trials with psychosis of AD inclusion criteria showed a significant effect on any psychosis subscale score.

Subgroup Analyses

For these analyses, the effect sizes for the main outcomes for each trial were standardized to one SD unit calculating a standardized mean difference (SMD) by meta-analysis for each drug, psychosis or not, inpatient versus outpatient status, and level of cognitive impairment (MMSE >10 or ≤10). We used the BPRS total for the aripiprazole, olanzapine, quetiapine 5077 US-039, one risperidone contrast (trial HGGU), the PANSS-EC for quetiapine 5077 US-039, the CMAI for one quetiapine trial, and the BEHAVE-AD for four risperidone trials.

The overall SMD by meta-analysis for the 14 available contrasts was −0.16 (95% CI: −0.24–−0.08; Z =

FIGURE 3. Efficacy on Psychosis Subscales (BPRS, NPI, and Behave-AD) by Subscale, by Drug by Comparison (weighted mean differences)



Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; WMD: weighted mean difference.

3.89, p = 0.0001). For aripiprazole, the SMD was −0.22 (95% CI: −0.36–−0.08; Z = 3.08, p = 0.002); for olanzapine, it was −0.11 (95% CI: −0.30–0.08; Z = 1.16, p = 0.25); for quetiapine, it was −0.17 (95% CI: −0.34–−0.01; Z = 2.05, p = 0.04); and for risperidone, it was −0.15 (95% CI: −0.32–0.03; Z = 1.62, p = 0.11) with significant heterogeneity for risperidone (χ^2 = 12.77, df = 4, p = 0.01, I^2 = 68.7%). When the HGGU outpatient trial using the BPRS with risperidone was removed, then the meta-analysis of the SMDs based on the BEHAVE-AD in the four nursing home trials (see Figure 1 for WMDs) becomes −0.18 (95% CI: −0.29–−0.08, Z = 3.43; p = 0.0006) still with heterogeneity of outcomes (χ^2 = 9.77, df = 3, p = 0.02, I^2 = 69.3%)

There were larger effect sizes for those without psychosis than those with psychotic symptoms (SMD of −0.24 versus −0.10, respectively; χ^2 = 4.26, df = 1, p = 0.04), larger effects for the 11 nursing home trials than the three outpatient trials (SMD of −0.19 versus −0.02; χ^2 = 3.90, df = 1, p = 0.05), and larger effects for the five trials with lower MMSE mean scores than the eight with higher (SMD of −0.26 versus −0.10; (χ^2 = 5.12, df = 1, p = 0.02).

Mini-Mental State Examination

Seven trials reported MMSE change scores: one aripiprazole, three olanzapine, one quetiapine, and two of five risperidone contrasts. The overall effect of drugs compared with placebo was a WMD of 0.73 (95% CI: 0.38–1.09, p <0.0001) in favor of placebo. All but one of the comparisons showed greater worsening for the drug group, with three statistically significant (Figure 8).

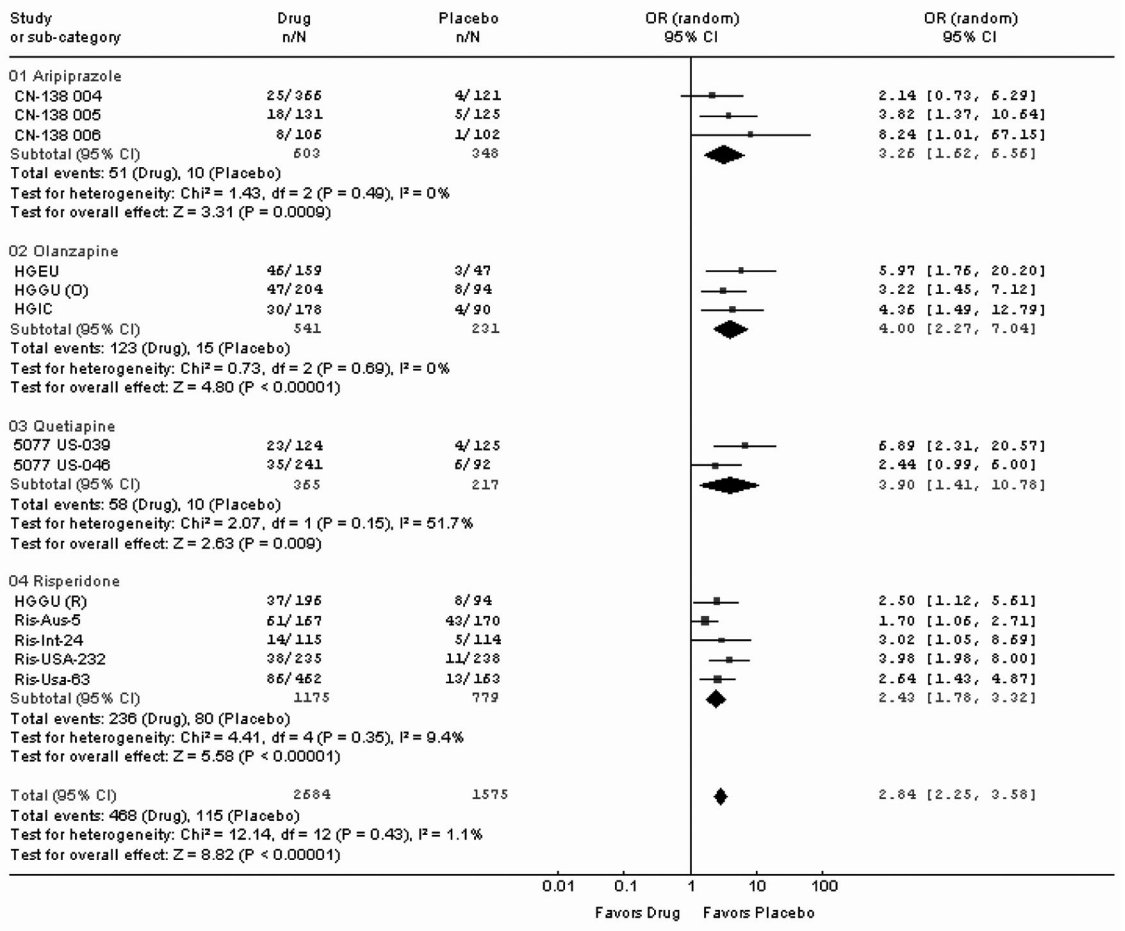
Adverse Events

Adverse events were inconsistently reported among the trials; most did not report adverse events occurring less than 10% or 5% of the time; potentially significant adverse events could not be counted from all trials. Somnolence, falls, injury, syncope, extrapyramidal effects, bruising (variously described as ecchymoses, purpura, hematoma, or contusions), edema, and urinary tract infections were reported from most trials. Data for cerebrovascular adverse events and deaths were obtained from additional sources.[13,17–19] Adverse events are summarized by the numbers of trials for which the event was reported and the odds ratio for the event.

Somnolence. The 13 available comparisons showed increased risk for somnolence with all but two statistically significant (Figure 4). The odds ratio by meta-analysis was 2.84 (95% CI: 2.25–3.58, p <0.00001), 17% versus 7% pooled rates, with significant heterogeneity. There was a significant risk difference between aripiprazole (RD: 0.06, 95% CI: 0.02–0.09) and olanzapine (RD: 0.16, 95% CI: 0.10–0.21).

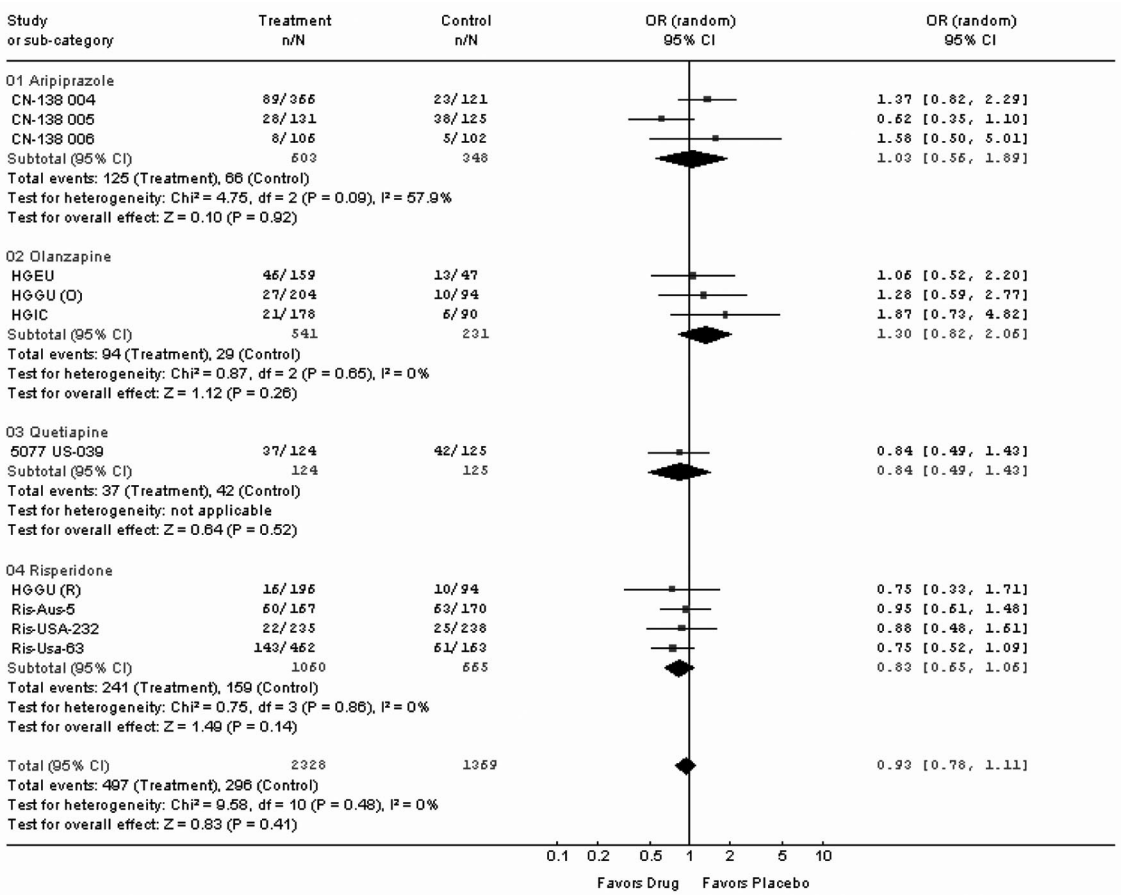
Injury or Falls. Outcomes are consistent in the 11 and eight contrasts that provided data for injury/accidental injury (Figure 5) and falls/syncope (data not shown) in not showing an increase or decrease in risks overall or the result of a particular drug or trial (OR: 0.93, 95% CI: 0.78–1.11, p = 0.41, 21% versus

FIGURE 4. Somnolence as Adverse Events by Drug by Comparison



Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; OR: odds ratio; n/N: number of events/total sample.

FIGURE 5. Injury and Accidental Injury as Adverse Events by Drug by Comparison



Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; OR: odds ratio; n/N: number of events/total sample.

22% pooled; OR: 0.98, 95% CI: 0.78–1.23, Z = 0.18, p = 0.86, 12% versus 15%, respectively).

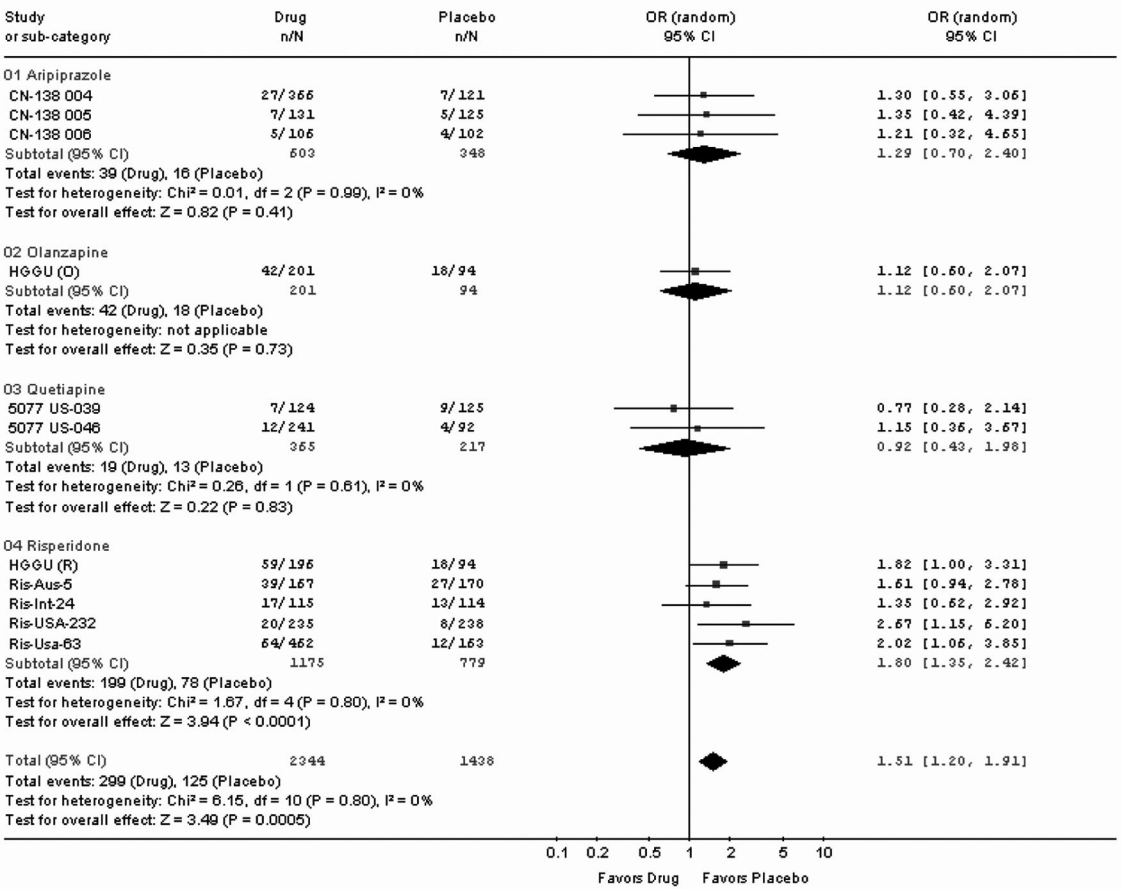
Extrapyramidal Effects. There was increased risk for EPS by meta-analysis (OR: 1.51, 95% CI: 1.20–1.91, p = 0.0005), 13% versus 8%, in the 11 contrasts with this data (Figure 6). The increased risk can be attributed to risperidone alone: for the risperidone trials, OR = 1.80 (95% CI: 1.35–2.42, p <0.0001), 17% versus 10% pooled with a risk difference by meta-analysis of RD: 0.06, 95% CI: 0.03–0.09.

Abnormal Gait. There was an overall increased risk for abnormal gait (OR: 3.42, 95% CI: 1.78–6.56, Z = 3.57, p = 0.0002), 10% versus 2% pooled for the five contrasts from four trials. There was increased risk in two olanzapine trials, two contrasts with risperidone, and no increased risk in one quetiapine trial.

Edema. There were increased risks by meta-analysis for edema (OR: 1.99, 95% CI: 1.20–3.30, Z = 2.65, p = 0.008), 9% versus 4% pooled, in the eight trials reporting. Two of three aripiprazole and the quetiapine trials did not report edema. The increased risk was associated with risperidone and olanzapine.

Urinary Tract Infections. Urinary tract infections (UTIs) were reported in eight contrasts but none with olanzapine (Figure 7). There was overall increased risk for UTIs in the antipsychotics-treated patients (OR: 1.28, 95% CI: 1.02–1.61, p = 0.04), 16% versus 12% pooled. The effect was not significant with any one drug, but only when the events were combined.

FIGURE 6. Extrapyramidal Signs and Symptoms as Adverse Events by Drug by Comparison



Note: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.
CI: confidence interval; OR: odds ratio; n/N: number of events/total sample.

The risk difference by meta-analysis was RD = 0.03 (95% CI: 0.00–0.05; Z = 1.91, p = 0.06). UTIs were not reported in the olanzapine trials (one included risperidone), but urinary incontinence was and was not reported in the trials of the other drugs. There was an overall increased risk for UTIs or urinary incontinence in 11 contrasts (OR: 1.51, 95% CI: 1.07–2.12, p = 0.02), 13% versus 10% pooled.

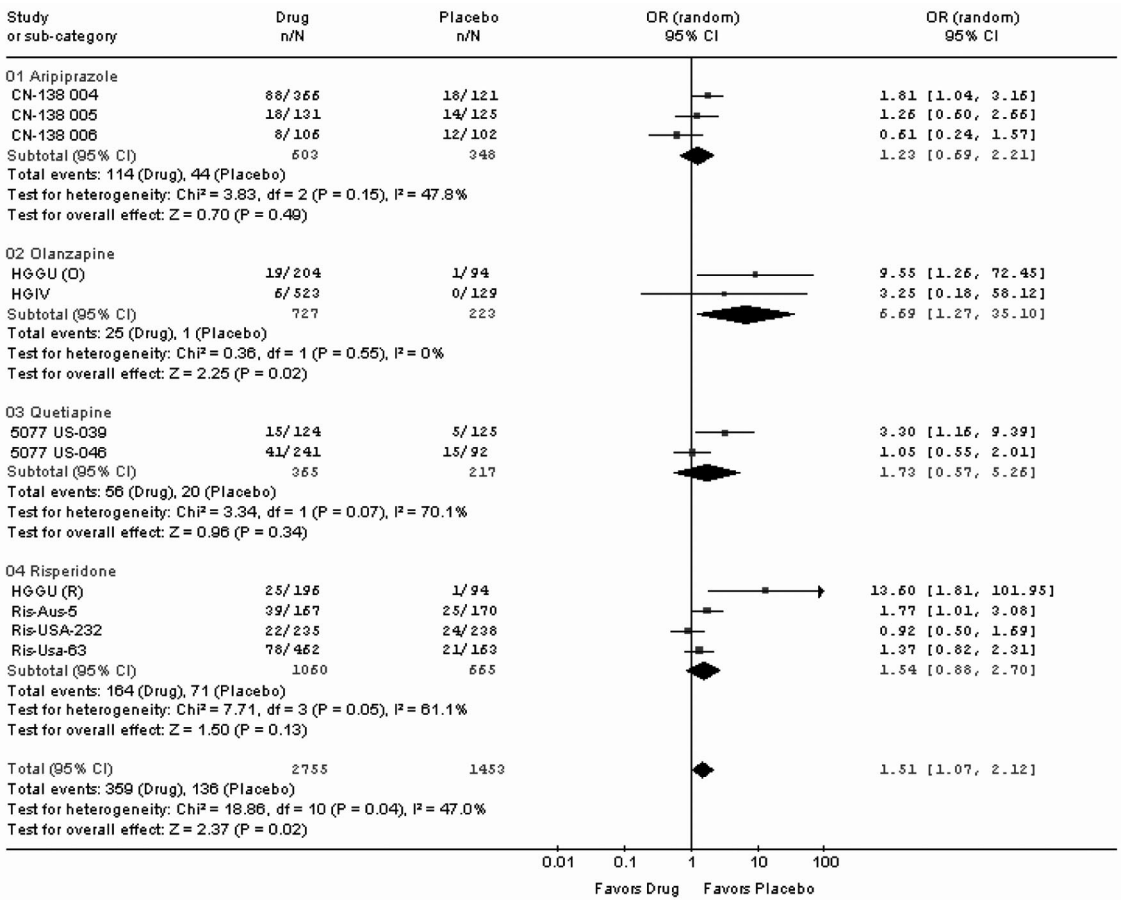
Cerebrovascular Adverse Events. Individual CVAEs were obtained through several sources.[17–19] There were 63 versus 16 events in drug and placebo patients, respectively, among 3,327 patients on drug and 1,728 on placebo. There was an increased OR by meta-analysis for CVAEs of 2.13 (95% CI: 1.20–3.75, Z = 2.60, p = 0.009), 1.9% versus 0.9% pooled. There was a significantly increased risk with risperidone (OR: 3.43, 95% CI: 1.60–7.32, Z = 3.18, p = 0.001), 3.1% versus 1.0% pooled.

Deaths. The overall OR by meta-analysis for death in patients treated with antipsychotics compared with placebo was reported previously[13] and was 1.54 (95% CI: 1.06–2.23; Z = 2.28, p = 0.02) pooled events of 3.5% versus 2.3%, drugs versus placebo. All but three trials showed rate differences in favor of placebo. There was no increased risk of death with any individual drug.

DISCUSSION

A considerable number of placebo-controlled trials of atypical antipsychotics for patients with dementia

FIGURE 7. Urinary Tract Infection or Urinary Incontinence as Adverse Events by Drug by Comparison



Notes: The trial HGGU placebo group is used for both risperidone and olanzapine comparisons. Olanzapine trials did not report urinary tract infections and reported urinary incontinence. Odds ratios for urinary tract infection only by meta-analysis for three aripiprazole, two quetiapine, and three risperidone comparisons (excluding olanzapine trials) is OR = 1.28 95% confidence interval: 1.02–1.61, Z = 2.09, p = 0.04, 16% versus 12%).

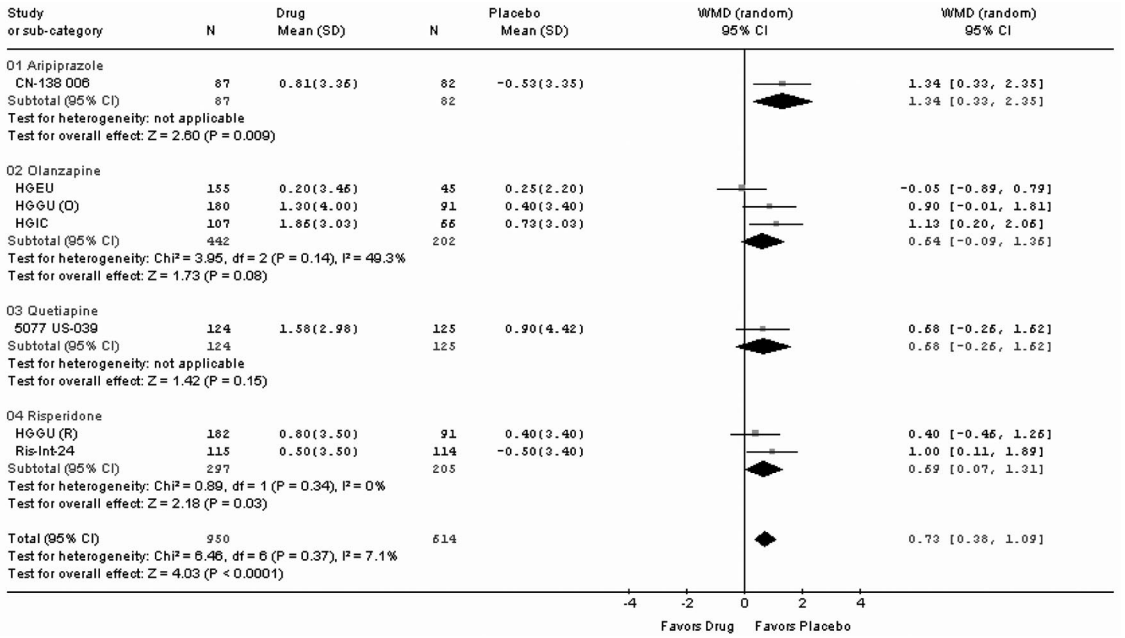
CI: confidence interval; OR: odds ratio; n/N: number of events/total sample.

have been undertaken and not all have been published, involving over 5,000 patients treated for generally 8–12 weeks. Patients on average were advanced in age, in their 80s, most had AD, and a minority cerebrovascular dementia. After statistically combining the trials there was evidence for symptomatic efficacy of aripiprazole and risperidone. Olanzapine was not associated with efficacy overall, and there was a lack of evidence for or against quetiapine because the three trials used different selection criteria and outcomes could not be statistically combined using a common rating scale.

Two of the three aripiprazole trials and the four risperidone trials were with nursing home patients. There was weak statistical evidence that nursing home residence or having greater cognitive impairment was associated with larger statistical effect sizes on selected outcomes compared with having lesser cognitive severity or being an outpatient. This evidence was gained, however, from sensitivity analyses in which selected outcomes were transformed to SMDs before combining them by meta-analysis.

An assumption in transforming to SMDs is that the metrics of the scales are sufficiently similar so that they can be validly combined. This probably is not the case, however, because the scales have different

FIGURE 8. Change in Mini-Mental State Examination Scores by Drug by Comparison



characteristics, items, scoring ranges, anchors, and clinical perspectives. Moreover, the trials are not directly comparable because of differences in selection criteria, dosing, and methodological differences among them as well. The use of SMDs here and in other meta-analyses nevertheless may serve the heuristic purposes of suggesting hypotheses and possible trends and effects to examine more fully.

The results of these analyses were a small statistical effect overall of −0.16 SD units, ranging between −0.11 and −0.22 for each of the four drugs individually. For any individual trial, the SMD was not higher than −0.25 except for one olanzapine and one risperidone nursing home trial with effects of −0.40 and −0.46, respectively. Similar or smaller statistical effect sizes would have been obtained if other outcomes had been transformed and combined. For example, combining the six trials (seven contrasts) that used NPI scores yielded an overall SMD of −0.10, ranging between −0.19 and −0.01 for each of the drugs. The magnitude of *statistical* effect, however, does not imply a similar magnitude *clinical* effect. For example, SMD differences of this magnitude are observed in meta-analyses of cognitive effects of cholinesterase inhibitors and memantine (for references, see the additional bibliography online).

For these reasons, we reviewed and analyzed each drug separately and by specific outcomes to better address the efficacy issue. In these analyses (Figure 1), mean differences between drug and placebo groups were observed of up to approximately 2.5 points on the BPRS, up to 3.6 points on the NPI, and approximately a mean 1.5 points on the BEHAVE-AD. Regardless of their nominal statistical significance, a fair question is whether or not these differences are *clinically significant*. Mean differences tell nothing about the individual patients who might benefit, whether any benefited greatly, or whether most benefited only slightly.

Ratings scales scores indicated, on average, moderate to severe behavioral symptoms with mean baseline BPRS total scores per trial ranging from 21–30, NPI total scores from approximately 34–43, and BEHAVE-AD scores from 16–19. Both the drugs and placebo groups improved considerably from baseline with the placebo groups improving approximately 5–7 points on average on the BPRS, 11–13 points on the NPI, and approximately 4 points on the BEHAVE-AD, representing approximately 25%–30% "in-trial" improvements with placebo and incrementally more improvement with drugs. Most improvement occurred within the first 2–4 weeks (data not

shown) and suggests that increased attention, nondrug interventions, and instability in symptoms were associated with improvement. It is not known whether improvement is sustained in patients throughout the trials, whether there is relapse, or whether others improve only later. Either with drugs or placebo, patients improved, but still had considerable symptoms *on average*. For example, the substantial majority of the patients treated with risperidone still would have met inclusion criteria for the trials.

Thus, the assessment of individual patient responses is needed to better address whether treatment is associated with clinically significant improvement. However, responders were reported in only 10 trials and were mainly defined arbitrarily based on a 30%, 40%, or 50% improvement from baseline values on ratings scales, although this technique still does not address potential clinical significance. Assessing responses with clinicians' global ratings begins to accomplish this because clinicians explicitly assess whether there has been clinically meaningful change.

Clinicians' global ratings were in fact used in all but one trial, yet the proportions of patients who improved or worsened could be obtained only from one quetiapine and two risperidone trials. Here the responses were 48% versus 30%, drug versus placebo, with the former and 65% versus 48% pooled with the two later trials. The 18% and 17% rate differences each imply a number needed to treat (NNT) of six patients need to be treated for one to respond as defined.

The effect sizes when the trials' authors defined response on the basis of 30%–50% improvements on several rating scales varied with rate differences of 0.07 or 0.10 pooled for two aripiprazole ratings from the same three trials (−0.04–0.20 from two olanzapine ratings from different trials; 0.08 and 0.09 from two quetiapine ratings from two trials; and −0.04 and 0.13 from two risperidone trials). The statistically significant comparisons (Figure 2) imply NNTs from five to 14 (NNTs cannot be defined for insignificant differences) but are calculated from selected ratings scales from selected trials and lack validity. The partial availability or reporting of response rates data suggests that smaller effects were not reported, especially for the global ratings.

The overall positive evidence for efficacy is mitigated by the dropout rates and adverse events. The one-third of patients who dropped out most likely was not gaining sufficient clinical benefits whether because of lack of efficacy or adverse events. Moreover, adverse events were inconsistently reported across trials. Rate differences for the events that were reported ranged from approximately 10% for somnolence to 1% for death, implying that the number of patients who need to be treated for one to have the adverse event range from 10 for somnolence to 100 for death. Adverse events such as somnolence, extrapyramidal motor system effects, or gait disturbances may have led to increased time spent in bed and possibly to the increased risk for UTIs or urinary incontinence, and possibly may have increased the risks for death resulting from infectious, pulmonary, or cardiovascular causes. Again, individual patient data are essential for further understanding. It is important to know how patients with adverse events were rated on the clinical scales. For example, a patient who had significant somnolence could have been rated improved on a rating scale.

A potentially reassuring aspect to the adverse events data are the evidence for no risks of falls or injury with drugs especially because there is a fairly substantial risk for falls or injury overall in this frail aged sample. This observation supports a hypothesis and analysis presented by Katz and colleagues[30] that a component of the effectiveness of risperidone is relative protection against the falls and injury associated with placebo, a therapeutic effect that would not be identified on symptom rating scales.

Most probably, other important adverse events were not identified either because they were not specifically sought or because they occurred less frequently than a critical threshold of 5% or 10% used for reporting purposes.

The atypicals clearly caused further cognitive impairment, an overall mean difference of nearly one MMSE point compared with placebo. By comparison, this is about the typical therapeutic effect of cholinesterase inhibitors on the MMSE (for references, see the additional bibliography online). This observation and the extent of somnolence suggest that the atypicals are causing deliria or confusional states in many patients. Causing further cognitive impairment is not good for patients, although it could be associated with both improvement and worsening on behavior rating scales. Conventional antipsychotics are associated in observational studies

with more rapid cognitive decline as well (for references, see the additional bibliography online)

It is possible that cholinesterase inhibitors might lessen the cognitive impairment associated with antipsychotics. It is notable that antipsychotics are generally not excluded medications in cholinesterase inhibitor trials. Conversely, patients receiving cholinesterase inhibitors may have less adverse cognitive effects from antipsychotics. The publications of appropriate secondary analyses from the cholinesterase inhibitor and memantine trials are needed.

LIMITATIONS

Meta-analyses are observational studies and are subject to various biases, including the complete ascertainment of trials performed, assessing the trials' qualities, deciding on the analytic protocol, information to be abstracted, studies to be combined, statistics, and interpretation of the results. Trials varied somewhat in their inclusion criteria. Patients included may have been restricted to AD or not, or on the basis of agitation or aggression or delusions or hallucinations. There were also differences in cognitive severity that resulted from the use of minimum cognitive criteria in some trials, especially those requiring that patients have symptoms of psychosis.

The dosing may not reflect how these drugs are typically prescribed. Some used fixed doses and others allowed dosage adjustment. By fixing doses and requiring that patients be kept on medication throughout the trial, many patients who may not be responding are also placed at increased risk for adverse events and do not have the potential to benefit from individualized dosing adjustments. By comparison, in clinical practice, medication might have been discontinued, increased, or switched. Thus, the clinical trials may reflect both more adverse events and less efficacy than patients actually experience. It is also possible that higher doses of medications contributed greater effect sizes for adverse events while not contributing to an efficacy effect size, and lower doses may have reduced the efficacy effect size. Our examination of dose–response effects was limited by the fact that there was only one dose-ranging trial each for aripiprazole and risperidone, the drugs that showed overall efficacy. Future trials need to be ecologically relevant to represent the clinical population needing treatment, the typical use of medications, and relevant outcomes.

All but one of these trials was sponsored by drug companies and were most probably performed in compliance with good clinical practice standards. Some were undertaken with a view toward obtaining regulatory approval for treating psychosis of AD. Thus, in their protocols' compliance and monitoring, they were most probably of good quality and relatively free of significant biases. The failure of some to specify and report adequately their main outcomes is a deficiency in quality.

PRACTICE IMPLICATIONS

The modest efficacy and uncertain response rates combined with the risks detailed here suggest that antipsychotics should be used with more deliberate consideration. Medications should be prescribed and adjusted to maximize efficacy while minimizing adverse events; the adverse event evidence coupled with the efficacy evidence suggests that the use of lower doses might be prudent and effective.

Clinical improvement should be expected well within 10 or 12 weeks, the length of the trials. If improvement is not seen, then medication should be discontinued, and other approaches, including revisiting or modifying behavioral and environmental interventions or another antipsychotic, could be considered. Moreover, because a substantial proportion of patients responding may be responding to in-study effects, increased nursing care, environmental changes, or changes in medical status, and not actually to medication, "n of one" trials of medication withdrawal could be undertaken at frequent intervals to assess continuing need.[13]

It would not be prudent to prescribe other medications in lieu of antipsychotics under a belief that they are as effective as or safer than atypicals. There is an absence of evidence for either efficacy or adverse events with nonantipsychotic drugs, and the existing trials are not adequate to detect either efficacy or increased risk at the statistical power reported here.[10]

Individual subject meta-analyses could potentially identify characteristics associated with clinical out-

comes or adverse effects, but requires obtaining databases from the trials' sponsors or authors. Considering that future trials are unlikely and antipsychotics do not have labeling for treating dementia, the drug manufacturers might be encouraged to allow their data to be combined and analyzed by independent organizations. This would ultimately benefit patients. Psychosis and aggression in people with dementia is a serious problem and is difficult to treat. Antipsychotics are modestly effective when used judiciously and there are no demonstrated, effective pharmacologic alternatives.

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References

1. Alexopoulos GS, Silver JM, Kahn DA, et al: The Expert Consensus Guideline Series: treatment of agitation in older persons with dementia. Postgrad Med 1998:1–88
2. Alexopoulos GS, Jeste DV, Chung H, et al: The Expert Consensus Guideline Series: treatment of dementia and its behavioral disturbances. Postgrad Med 2005:1–111
3. Katz IR, Jeste DV, Mintzer JE, et al: Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999; 60:107–115
4. De Deyn PP, Rabheru K, Rasmussen A, et al: A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999; 53:946–955
5. Street JS, Clark WS, Gannon KS, et al: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2000; 57:968–976
6. Brodaty H, Ames D, Snowdon J, et al: A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003; 64:134–143
7. De Deyn PP, Carrasco MM, Deberdt W, et al: Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19:115–126
8. Ballard C, Margallo-Lana M, Juszczak E, et al: Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ 2005; 330: 874–877
9. Deberdt WG, Dysken MW, Rappaport SA, et al: Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry 2005; 13:722–730
10. Sink KM, Holden KF, Yaffe K: Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005; 293:596–608
11. Chan W, Lam L, Choy C, et al: A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001; 16:1156–1162
12. Tariot PN, Schneider LS, Katz IR, et al: Quetiapine in nursing home residents with Alzheimer's dementia and psychosis. Poster presented at the 15th Annual Meeting of the American Association for Geriatric Psychiatry; Feb 24–27; Orlando, Fla. Am J Geriatr Psychiatry 2002; 10(suppl 1):93.
13. Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294:1934–1943
14. Health Canada Therapeutic Products Directorate, Risperdal warning letter. Oct 11, 2002. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2002/risperdal_hpc-cps_e.html.
15. The Cochrane Library, Issue 1, 2005. Chichester, UK, John Wiley & Sons Ltd, 2005
16. Jeste DV, Finkel SI: Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 2000; 8:29–34
17. Racoosin JA: Evaluating a safety signal in the postmarking period: cerebrovascular adverse events associated with risperidone and olanzapine. Paper presented at the 17th Annual Meeting of the American Association for Geriatric Psychiatry; Feb 21–24, 2004; Baltimore
18. Bristol-Myers Squibb Medical Letter. Labeling Change for Abilify on Risk of CVA in Elderly. Feb 10, 2005
19. Schneider LS, Tariot PN, Mintzer J, et al: Cerebrovascular adverse events and quetiapine: a pooled analysis in elderly patients with dementia. Paper presented at the 18th Annual Meeting of the American Association for Geriatric Psychiatry; March 3–6, 2005; San Diego
20. Review Manager (RevMan) [computer program]. Version 4.2. Oxford, UK, The Cochrane Collaboration, 2004
21. Howanitz E, Wisotzek I: Olanzapine versus placebo in the treatment of behavioral disturbances associated with vascular dementia. Poster presented at the 14th Annual Meeting of the American Association for Geriatric Psychiatry; Feb 23–26, 2001; San Francisco
22. Satterlee WG, Reams SG, Burns PR, et al: A clinical update on olanzapine treatment in schizophrenia and in elderly Alzheimer's disease patients. Psychopharmacol Bull 1995; 31:534
23. Reisberg B, Borenstein J, Salob SP, et al: Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987; 48(suppl):9–15
24. Cohen-Mansfield J, Marx MS, Rosenthal AS: A description of agitation in a nursing home. J Gerontol 1989; 44:M77–84
25. Overall JE, Beller SA: The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research: I. Factor structure on an inpatient unit. J Gerontol 1984; 39:187–193
26. Cummings JL, Mega M, Gray K, et al: The Neuropsychiatric

Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308–2314
27. Guy W: Clinical Global Impressions (CGI), In ECDEU Assessment Manual for Psychopharmacology. 1976:218–222
28. Schneider LS, Olin JT, Doody RS, et al: Validity and reliability of the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11(suppl 2): S22–32
29. Alexopoulos GS, Abrams RC, Young RC, et al: Cornell Scale for Depression in Dementia. Biol Psychiatry 1988; 23:271–284
30. Katz IR, Rupnow M, Kozma C, et al: Risperidone and falls in ambulatory nursing home residents with dementia and psychosis or agitation: secondary analysis of a double-blind, placebo-controlled trial. Am J Geriatr Psychiatry 2004; 12:499–508
31. Breder C, Swanink R, Marcus R, et al: Dose-ranging study of aripiprazole in patients with Alzheimer's dementia. Poster presented at the 9th International Conference on Alzheimer's Disease and Related Disorders; July 17–22, 2004; Philadelphia
32. Streim J, Breder C, Swanink R, et al: Flexible dose aripiprazole in psychosis of Alzheimer's dementia (AD). Poster presented at the 157th American Psychiatric Association Annual Meeting; May 1–6, 2004; New York
33. Kujawa M, Marcus R, Breder C, et al: Safety profile of aripiprazole in psychosis of Alzheimer's dementia: pooled analysis. Poster presented at the 9th International Conference on Alzheimer's Disease and Related Disorders; July 17–22, 2004; Philadelphia
34. Stock E, Breder C, Goyvaerts H, et al: Safety profile of aripiprazole in psychosis of Alzheimer's dementia: pooled analysis. Poster presented at the American Psychiatric Association Annual Meeting; May 1–6, 2004; New York
35. De Deyn PP, Jeste DV, Mintzer JE, et al: Aripiprazole in dementia of the Alzheimer's type. Poster presented at the 16th Annual Meeting American Association for Geriatric Psychiatry; March 1–4, 2003; Honolulu
36. Street JS, Tollefson GD, Tohen M, et al: Olanzapine for psychotic conditions in the elderly. Psychiatric Annals 2000; 30:191–196
37. Street JS, Kinon B, Stauffer V: Olanzapine in dementia, in Olanzapine (Zyprexa): A Novel Antipsychotic. Edited by Tran PV. Philadelphia, Lippincott Williams & Wilkins, 2000, pp 416–426
38. Cavazzoni P, Young CA, Polzer J, et al: Incidence of cerebrovascular adverse events and mortality during antipsychotic clinical trials of elderly patients with dementia. Poster presented at the 44th Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting (modifications added); June 1–4, 2004; Phoenix
39. Deberdt W, Dysken MW, Rappaport SA, et al: Placebo-controlled comparison of olanzapine and risperidone in the treatment of psychosis and behavioral disturbances in patients with dementia. Poster presented at the American Geriatrics Society; May 17–21, 2004; Las Vegas
40. Kennedy JS, Young CA, Hoffman VP, et al: A placebo-controlled 10-week prospective comparison of the occurrence of falls in dementia: olanzapine versus risperidone. Poster presented at the International College of Geriatric Psychoneuropharmacology; Oct 10–12, 2002; Barcelona, Spain
41. Kennedy JS, Deberdt W, Micca J, et al: The effect of olanzapine on cognition in patients with Alzheimer's disease without psychosis or agitation. Poster presented at the International College of Geriatric Psychoneuropharmacology; Oct 14–16, 2004; Basel, Switzerland
42. Zhong K, Tariot P, Minkwitz M, et al: Quetiapine for the treatment of agitation in elderly institutionalized patients with dementia: a randomized, double-blind trial. Poster presented at the 9th International Conference on Alzheimer's Disease and Related Disorders; July 17–22, 2004; Philadelphia
43. De Deyn PP, DeSmedt G: Risperidone in the treatment of behavioral disturbances in elderly patients with dementia. Poster presented at the Eighth Congress of the International Psychogeriatric Association; Aug 17–22, 1997; Jerusalem
44. Mintzer J, Weiner M, Greenspan A, et al: Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer's disease. Poster presented at the International College of Geriatric Psychopharmacology; Oct 14–17, 2004; Basel, Switzerland

SUPPLEMENTAL ONLINE BIBLIOGRAPHY

Predictors of Cognitive Decline

McShane R, Keene J, Gedling K, et al: Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. BMJ 1997; 314:266–270

Chui HC, Lyness SA, Sobel E, et al: Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer disease. Arch Neurol 1994; 51:676–681

Drevets W, Rubin E: Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. Biol Psychiatry 1989; 25:39–48

Lopez O, Becker J, Brenner R, et al: Alzheimer disease with delusions and hallucinations: neuropsychological and electroencephalographic correlates. Neurology 1991; 41:906–912

Stern Y, Albert M, Brandt J, et al: Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer disease: prospective analyses from the Predictors Study. Neurology 1994; 44:2300–2307

Stern Y, Mayeux R, Sano M, et al: Predictors of disease course in patients with probable Alzheimer disease. Neurology 1987; 37:1649–1653

References to Cerebrovascular Adverse Events

Wooltorton E: Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 2002; 167:1269–1270

Medicines and Health Care Products Regulatory Agency (UK): Summary of clinical trial data on cerebrovascular adverse events (CVAEs) in randomized clinical trials of risperidone conducted in patients with dementia. March 9, 2004. Available at: http://medicines.mhra.gov.uk

Safety data on Zyprexa (olanzapine)—Hyperglycemia and Diabetes. March 1, 2004. Available at: http://www.fda.gov/medwatch/SAFETY/2004/zyprexa.htm

Wooltorton E: Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. CMAJ 2004; 170:1395

Racoosin JA: Evaluating a safety signal in the postmarking period: cerebrovascular adverse events associated with risperidone and olanzapine. Paper presented at the 17th Annual Meeting of the American Association for Geriatric Psychiatry; February 21–24, 2004; Baltimore

Reviews of Treatment of Psychosis and Aggression in Dementia

Sink KM, Holden KF, Yaffe K: Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005; 293:596–608

Lee PE, Gill SS, Freedman M, et al: Atypical antipsychotic drugs in the treatment of behavioral and psychological symptoms of dementia: systematic review. BMJ 2004; 329:75

Lanctot KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. J Clin Psychiatry 1998; 59:550–561

Kindermann SS, Dolder CR, Bailey A, et al: Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging 2002; 19:257–276

Schneider LS, Dagerman KS: Psychosis of Alzheimer disease: clinical characteristics and history. J Psychiatr Res 2004; 38:105–111

Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990; 38:553–563

References to Statistical Analyses

DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–188

Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719–748

Higgins J, Thompson S, Deeks J, et al: Measuring inconsistency in meta-analysis. BMJ 2003; 327:557–560

Hedges L, Olkin I: Statistical Methods for Meta-Analysis. San Diego, CA, Academic Press, 1985

Cholinesterase Inhibitors and Memantine

Birks JS, Harvey R: Donepezil for dementia due to Alzheimer disease. Cochrane Database Syst Rev 2003; 3:1–100

Birks J, Grimley Evans J, Iakovidou V, et al: Rivastigmine for Alzheimer disease. Cochrane Database Syst Rev 2000; 4:1–126

Loy C, Schneider L: Galantamine for Alzheimer disease. Cochrane Database Syst Rev 2004; 4:1–75

Areosa SA, Sherriff F, McShane R: Memantine for dementia. Cochrane Database Syst Rev 2005; 3:1–77

McShane R, Schneider LS: Meta-analysis of memantine: summary and commentary on the Cochrane Collaberation's systematic review. Alzheimer Dementia 2005; 1:67–71