Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia

Meta-analysis of Randomized Placebo-Controlled Trials

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Context Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease and other dementia; however, concerns have arisen about the increased risk for cerebrovascular adverse events, rapid cognitive decline, and mortality with their use.

Objective To assess the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia.

Data Sources MEDLINE (1966 to April 2005), the Cochrane Controlled Trials Register (2005, Issue 1), meetings presentations (1997-2004), and information from the sponsors were searched using the terms for atypical antipsychotic drugs (*aripiprazole*, *clozapine*, *olanzapine*, *quetiapine*, *risperidone*, and *ziprasidone*), *dementia*, *Alzheimer disease*, and *clinical trial*.

Study Selection Published and unpublished randomized placebo-controlled, parallel-group clinical trials of atypical antipsychotic drugs marketed in the United States to treat patients with Alzheimer disease or dementia were selected by consensus of the authors.

Data Extraction Trials, baseline characteristics, outcomes, all-cause dropouts, and deaths were extracted by one reviewer; treatment exposure was obtained or estimated. Data were checked by a second reviewer.

Data Synthesis Fifteen trials (9 unpublished), generally 10 to 12 weeks in duration, including 16 contrasts of atypical antipsychotic drugs with placebo met criteria (aripiprazole [n=3], olanzapine [n=5], quetiapine [n=3], risperidone [n=5]). A total of 3353 patients were randomized to study drug and 1757 were randomized to placebo. Outcomes were assessed using standard methods (with random- or fixed-effects models) to calculate odds ratios (ORs) and risk differences based on patients randomized and relative risks based on total exposure to treatment. There were no differences in dropouts. Death occurred more often among patients randomized to drugs (118 [3.5%] vs 40 [2.3%]. The OR by meta-analysis was 1.54; 95% confidence interval [CI], 1.06-2.23; $P=.02$; and risk difference was 0.01; 95% CI, 0.004-0.02; $P=.01$). Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis.

Conclusions Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives. Individual patient analyses modeling survival and causes of death are needed.

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A MAJORITY OF ELDERLY PATIENTS with dementia develop aggression, delusions, and other neuropsychiatric symptoms during their illness course. Antipsychotic medications are commonly used to treat these behaviors, along with psychosocial and environmental interventions. They have been the mainstay of psychopharmacological treatment for this purpose during the last several decades despite their clear overuse in the 1980s and federal regulations implemented in the early 1990s requiring their oversight and monitoring in nursing homes.[1]

During the last decade, the newer atypical antipsychotic drugs (ie, risperidone, olanzapine, quetiapine, and aripiprazole, in order of introduction) have largely replaced the older conventional or first-generation antipsychotic drugs (eg, haloperidol and thioridazine) and have been considered preferred treatments for these behavioral disturbances associated with dementia.[2,3] Reasons for this preference include emerging clinical trials evidence,[4-8] perceived relative safety advantages compared with older antipsychotic drugs and other medications, the opinions of expert clinicians, and ex-

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pectations of efficacy.[2,3] There is little clinical trials evidence supporting the efficacy of other classes of psychotropic medication, such as benzodiazepines, anticonvulsants, and antidepressants, for the treatment of aggression, psychotic symptoms, or agitation in patients with dementia.[9]

The perceived relative safety advantages of atypical drugs compared with conventional antipsychotic drugs or other medications include lesser cardiovascular adverse effects (eg, orthostatic hypotension and repolarization delays), less sedation, postural instability, falls, movement disorders, and thermodysregulation. The few direct comparison trials, however, are inadequate to address this.[5,10-12] Moreover, both conventional antipsychotic use and the presence of psychotic symptoms have been associated with more rapid cognitive decline in patients with dementia.[13-18]

Recently, there has been concern about an increased risk for cerebrovascular adverse events (mainly stroke and transient ischemic episodes, and some instances of loss of consciousness or syncope), metabolic syndrome, and other adverse events that may be specifically caused by certain atypical drugs.[19-22] The evidence for cerebrovascular adverse events was found through pooled analyses of mainly nursing home clinical trials of risperidone and olanzapine for people with dementia performed by regulators who had access to unpublished data.[20,23] These analyses assessing incidences during clinical trials all show increased relative risks (RRs) or odds ratios (ORs) ranging from 2 to 4, albeit with some not reaching nominally statistically significant *P* values.

Health Canada advised Canadian physicians in late 2002 "to reassess the risks and benefits . . . in elderly patients with dementia . . . [and to] counsel their patients/caregivers to immediately report signs and symptoms of potential cerebrovascular adverse events so that diagnosis can be made and treatment options considered. . . . "[24] The US Food and Drug Administration (FDA) followed with additional warnings of increased cerebrovascular adverse events to the US prescribing information for risperidone in April 2003 (http://www.risperdal.com), olanzapine in January 2004 (http://www.zyprexa.com), and aripiprazole in February 2005 (http://www.abilify.com). There is limited public access to these data, however, because most of the trials have not been published, cerebrovascular adverse events were not reported in some trials, and adverse events occurring less than 5% of the time are often not reported.

Deaths during antipsychotic clinical trials may be consequent to an adverse event caused by the drugs, and because they are classified by federal regulation as "serious adverse events"[25] are generally included in clinical trials reports. At a medical conference in 2002, the FDA reported on deaths occurring in a sample of 1452 patients with dementia from placebo-controlled trials of atypical antipsychotic drugs (approximately 32% received placebo, 59% atypical drugs, and the rest mostly received haloperidol). There was a high rate of deaths in the placebo group (164.7 per 1000 patient-years) and higher rates of 242.5 and 276.3 per 1000 patient-years for atypical and conventional drugs,[26] respectively, implying RRs of 1.47 and 1.68 for atypical and conventional drugs, respectively, compared with placebo. On April 11, 2005, the FDA issued a health advisory warning of an increased risk for death with atypical drugs in persons with dementia but did not provide data.[27] Despite the FDA warning and a lack of controlled trials proving efficacy, consultants found atypical antipsychotic drugs beneficial in calming agitated or aggressive elderly patients and noted that there were no good alternatives.[28]

In light of these events and the expanding evidence base, we conducted independent individual study meta-analyses of atypical antipsychotic drug trials to assess the evidence for mortality associated with their use in elderly patients with dementia.

METHODS

Search Strategy, Trials Selection, and Data Retrieval

MEDLINE (1966 to April 2005) and the Cochrane Controlled Trials Register (2005, Issue 1)[29] were searched, using the terms *aripiprazole*, *clozapine*, *olanzapine*, *quetiapine*, *risperidone*, and *ziprasidone* (atypical antipsychotic drugs marketed in the United States), *dementia*, *Alzheimer disease*, and *clinical trial*. Conference programs, abstract books, proceedings, Web postings from available conferences, proceedings, abstracts, poster presentations, and slides from geriatric medicine, psychiatric, neurological, and geriatric psychiatric professional society meetings since 1999 were handsearched. Pharmaceutical manufacturers were queried and information was requested as needed.

Trials were included in the study analyses if they met the following criteria: parallel group, double-blinded, placebo-controlled with random assignment to an orally administered antipsychotic or placebo; patients had Alzheimer disease, vascular dementia, mixed dementia, or a primary dementia; and numbers of patients randomized, dropouts, and deaths were obtainable. Additional information had to be available with respect to sample selection criteria, location of patients, randomization, double-blinding, trials durations, medication dosage ranges and formulations, and outcomes. Trials did not need to be published or peer-reviewed and could be reported in manuscripts, technical trials reports, posters, letters, or slide formats. (Some sources presented incomplete information and additional information was obtained though other data presentations or from sponsors).

Information extracted included design, selection criteria (dementia diagnoses and presence of psychosis of dementia[30]), medication doses, locations, trials durations, age, sex, baseline cognitive scores, numbers randomized, and the outcomes, all-cause dropouts, and deaths occurring during the double-blind trial period or within 30 days of

discontinuing double-blind treatment. Because there were few dose-ranging trials, sparse outcomes, and to avoid multiple comparisons with the same placebo group, we aggregated dosage groups within each trial to make one contrast with the placebo group. Data were abstracted by one investigator (K.S.D.) and checked by another investigator (P.I.). Any discrepant data were rereviewed by the investigators to ensure that accurate data were obtained.

After the trials to be included were identified, we extracted or calculated total drug and placebo exposure duration (patient-years of treatment) after noticing that this information could be obtained from several sources, including a presentation by the FDA,[23] a manuscript under review,[31] a "letter to health care professionals" from a pharmaceutical company,[32] and any information that could be estimated from another article.[33]

Statistical Analyses

The dropouts or deaths and the number randomized into each drug and placebo for each trial were statistically combined using the DerSimonian and Laird random-effects model for dropouts and the Mantel-Haenszel fixed-effects model for deaths. Effects were expressed as ORs and absolute risk differences with their 95% confidence intervals (CIs) and *P* values using Review Manager version 4.2.7 software (The Cochrane Collaboration, Oxford, England). Effects were calculated for each drug-placebo contrast, as meta-analytic summaries for each drug, and for all atypical drugs combined. A funnel plot in which sample size was plotted against the log OR of the outcome was used to evaluate potential retrieval bias and to compare the published trials with the nonpublished trials.

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 due to heterogeneity rather than sampling error.[34] An α error $P \leq .20$ and I^2 of at least 50% were taken as indicators of heterogeneity of outcomes.

We compared the following subgroups as sensitivity analyses: whether or not sample selection required that patients had to have psychosis of dementia,[30] outpatient vs nursing home status, cognitive severity (mean baseline Mini-Mental State Examination score per trial >10 or ≤ 10), or by drug used. Differences between 2 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 a *df* of 1 less than the number of subgroups.[35]

As an additional analysis, rates for deaths were expressed as the number of events divided by total duration of exposure to drug or placebo in patient-years and RRs were calculated for each drug and summarized by meta-analysis using a random-effects model.

RESULTS

Search Flow

The search strategy yielded 352 MEDLINE citations and 118 Cochrane Controlled Trials Register citations. A total of 27 MEDLINE and 24 Cochrane Controlled Trials Register citations were retrieved as likely placebo-controlled trials, from which 5 and 6 citations, respectively, were retained as fulfilling search criteria (FIGURE 1). One placebo-controlled trial of olanzapine (n=16 patients)[36] was not included because the only available documentation was an abstract with inadequate information. The 6 trials from the Cochrane results included the 5 trials from MEDLINE; 5 were primary trial articles, 1 was a review with information about an olanzapine trial not contained elsewhere.[37] 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.[33]

Twenty-four posters and slide presentations from medical conferences were obtained, which contained information on placebo-controlled trials, and 13 with unique information on 10 trials were retained.

From other sources, including medical letters and direct communications from pharmaceutical companies and news articles in medical journals, 18 placebo-controlled, randomized controlled 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), one 12-week-long multicenter nursing home trial terminated early (RIS-INT-83, n=18), and one 12-week-long outpatient trial in Germany, which used heterogeneous, patients with "organic psychosis syndrome" (RIS-GER-16, n=815) (A. Greenspan, Janssen Pharmaceuticals Inc, written communication, December 7, 2004). No other placebo-controlled trials of atypical drugs in patients with dementia were identified.

Trials and Patient Characteristics

Fifteen trials fulfilled criteria and were included in the review (TABLE).[4-8,11,12,33,37-51] These trials included 3 aripiprazole trials, 2 in nursing homes and 1 with outpatients (10-week durations); 5 olanzapine trials, 2 in nursing homes, 3 with outpatients, and 1 with a risperidone comparison (6- to 26-week durations); 5 risperidone trials, including the outpatient trial above with an olanzapine comparison, 4 in nursing homes, 1 with a haloperidol comparison (8- to 12-week durations); and 3 quetiapine nursing homes trials, 1 with a haloperidol comparison and another with rivastigmine (10- to 26-week durations). One trial is counted both as a risperidone trial and an olanzapine trial. Thus, 11 trials were performed in nursing homes and 4 with outpatients. Eight trials allowed dosage adjustment, 2 trials were fixed-dose, and 5 trials were dose-ranging with 2 or 3 fixed doses of study drug.

Overall, 3353 patients were randomized to drug (603 were randomized to aripiprazole, 1184 to olanzapine, 391

to quetiapine, and 1175 to risperidone) and 1757 were randomized to placebo. In 2 trials, one comparing quetiapine and the other comparing risperidone with haloperidol and placebo, 293 were randomized to haloperidol.

Overall, 87% of all patients had Alzheimer disease; the weighted mean (SD) age per trial was 81.2 (7.8) years; and 70% were women. Nine trials allowed patients with Alzheimer disease only and comprised 53% of the patients; 6 allowed patients to have various dementia diagnoses and included 73% of patients with Alzheimer disease. The extent of cognitive impairment ranged from mild to severe with 13 trials having mean Mini-Mental State Examination scores of 11.3 (range of means per trial, 5.4-21.5) on a 30-point scale.

Meta-analysis Outcomes

We found 118 deaths in the atypical antipsychotic drug groups and 40 in the placebo groups, a simple pooled incidence of 3.5% and 2.3% per trial, respectively. The overall OR by meta-analysis for death in patients treated with antipsychotic drugs compared with placebo was 1.54 (95% CI, 1.06-2.23; $P=.02$), and the risk difference was 0.01 (95% CI, 0.004-0.02; $P=.01$). There was no significant heterogeneity among the outcomes (for OR: $\chi^2_{15}=8.45$, $P=.90$, and for risk difference: $\chi^2_{15}=13.63$, $P=.55$; $I^2=0\%$ for both analyses; FIGURE 2). A funnel plot graphing log ORs against sample size did not show evidence of selection bias with symmetry around the mean overall effect, or asymmetry between published and unpublished trials (data not shown).

The risk differences for death in patients treated with aripiprazole vs placebo were 0.01 (95% CI, –0.01 to 0.03; $P=.20$); for olanzapine vs placebo, 0.01 (95% CI, –0.00 to 0.03; $P=.07$); for quetiapine vs placebo, 0.02 (95% CI, –0.01 to 0.05; $P=.22$); and for risperidone vs placebo, 0.01 (95% CI, –0.01 to 0.02; $P=.33$). All but 3 trials showed risk differences in favor of the placebo group.

We found 1079 all-cause dropouts (32.2%) among the drug-treated groups and 551 (31.4%) among the placebo-treated groups (FIGURE 3). Overall, there was no significant difference in dropouts by meta-analysis, although there was significant heterogeneity among dropouts from trial to trial and drug to drug ($\chi^2_{15}=30.89$, $P=.009$; $I^2=51.4\%$). The risk differences for dropouts in patients treated with aripiprazole vs placebo were –0.07 (95% CI, –0.15 to 0.01; $P=.10$); for olanzapine vs placebo, 0.06 (95% CI, –0.02 to 0.15; $P=.12$); for quetiapine vs placebo, 0.02 (95% CI, –0.08 to 0.11; $P=.73$); and for risperidone vs placebo, 0.03 (95% CI, –0.03 to 0.08; $P=.31$). The weak statistical trends for more patients receiving olanzapine vs placebo and fewer patients receiving aripiprazole vs placebo to dropout may have contributed to the overall heterogeneity of the effects. There was no association between risk for death per contrast with dropouts per contrast (log OR of death vs log OR of dropouts: $r=0.23$, $df=14$, $P=.40$).

Subgroup analyses did not reveal heterogeneity between trials of patients of higher cognitive function (Mini-Mental State Examination score >10) compared with lower cognitive function,

Figure 1. Trials Identification and Selection Process

RCT indicates randomized controlled trial.

Table. Characteristics of Placebo-Controlled Trials and Patients Included in the Analyses

Source*	No. of Patients Randomized	Key Inclusion Criteria	Daily Medication Dose, mg	Location	Duration, wk	Age, Mean (SD) [Range], y	Women, %	MMSE Score, Mean (SD)
Aripiprazole								
CN 138-004[38]	487	AD with psychosis	2, 5, and 10 dose groups	Nursing home	10	82.5 [56-97]	79	12.4 (4.4)
CN 138-005[39-41]	256	AD with psychosis	2-15 (mean, 8.6)	Nursing home	10	83 [59-96]	76	12.9
CN 138-006[40-42]	208	AD with psychosis	2-15 (mean, 10)	Outpatient	10	81.5 (6.5) [56-99]	72	13.6 (4.3)
Olanzapine								
HGAO[37,43-45]	238	AD with psychosis	1-8 (modal dose, 2.4)	Outpatient	8	78.6 [64-94]	66	NA
HGEU[6,45]	206	AD with agitation, delusions, or hallucinations, not bedridden	5, 10, and 15 dose groups	Nursing home	6	82.8 (6.6) [61-97]	61	6.7 (6.4)
HGGU[45-47]	494	Dementia with hallucinations or delusions (78% AD, 5% vascular dementia, 17% mixed)	2.5-10 (mean, 5.2); risperidone: 0.5-2 (mean, 1.0)	Outpatient	10	78.4 (7.4)	66	14.5 (5.6)
HGIC[45,48]	268	AD, nonpsychotic, nonagitated, nondepressed, MMSE score of 14-26	5	Outpatient	26	78 (8.0)	56	21.5 (3.6)
HGIV[8,45]	652	AD with delusions or hallucinations	1, 2.5, 5, and 7.5 dose groups	Nursing home	10	76.6 (10.4)	75	13.7 (5.1)
Quetiapine								
Ballard[33]	80	AD with agitation	50-100; also rivastigmine: 6-12	Nursing home	26	83.8 (7.7)	80	NA
5077 US-039[11,12]	378	Elderly patients with psychosis, not bedridden (75% AD, 15% vascular dementia, 10% other)	25-600 (median, 97); haloperidol: 0.5-12 (median, 1.9)	Nursing home	10	83.9 (6.5) [66-99]	73	12.8 (5.4)
5077 US-046[49]	333	Dementia with agitation (73% AD, 7% vascular dementia, 8% mixed)	100 and 200 dose groups	Nursing home	10	83.2 (7.5)	74	5.4 (4.0)
Risperidone								
RIS-AUS-05[7]	345	Dementia with aggression, MMSE score of ≤23 (58% AD, 29% vascular demetia, 13% mixed)	0.50-2 (mean, 0.95)	Nursing home	12	82.7 (7.1)	71	5.3 (8.0)
RIS-INT-24[5,50]	344	Dementia, MMSE score of ≤23, BEHAVE-AD scale ≥8 (67% AD, 26% vascular dementia, 7% mixed)	0.50-4 (mean, 1.1); haloperidol: 0.50-4 (mean, 1.2)	Nursing home	12	81 [56-97]	56	8.4 (7.8)
RIS-USA-63[4]	625	Dementia, MMSE score of ≤23, BEHAVE-AD scale ≥8 (73% AD, 15% vascular dementia, 12% mixed)	0.5, 1, and 2 dose groups	Nursing home	12	82.7 (7.7)	68	6.6 (6.3)
RIS-USA-232[51]	473	AD with psychosis, MMSE score of 5-23, ambulatory with assistance	0.5-1.5 (mean, 1.0)	Nursing home	8	83.3 (7.3)	77	13.2 (5.0)

Abbreviations: AD, Alzheimer disease; BEHAVE-AD, Behavioral Pathology in Alzheimer Disease Rating Scale (a rating scale for behavioral symptoms); MMSE, Mini-Mental State Examination; NA, not assessed.
*Unique identification code, which identifies the study or the collection of posters, abstracts, unpublished manuscripts, or published trials of the study drug.

patients with psychosis of Alzheimer disease compared with those trials that did not select patients on this basis, trials that included inpatients compared with outpatients, or among the 4 drugs included.

Ad Hoc Analyses

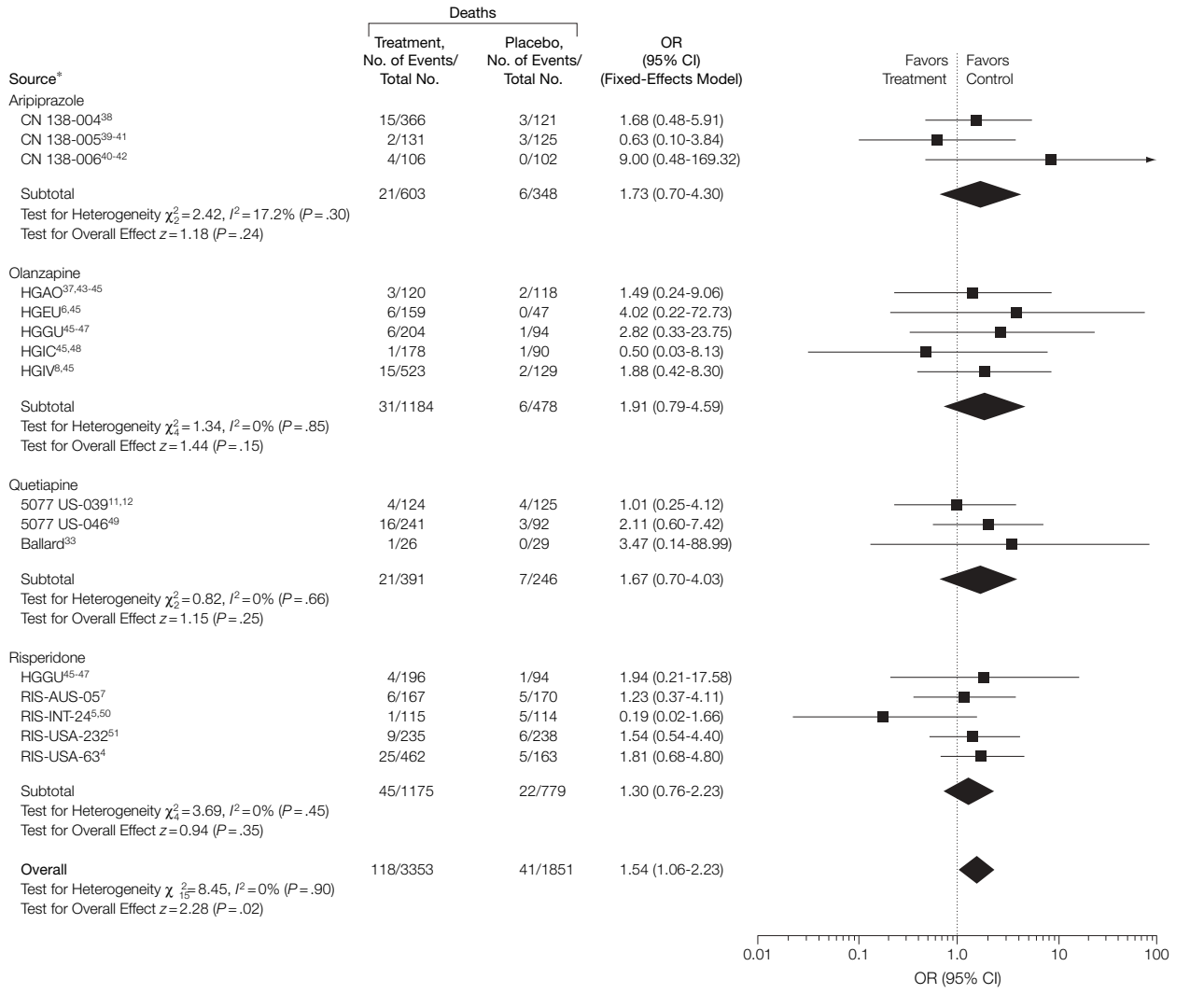
Using available data on total exposure to drug or placebo, we calculated RRs for death by pooling data for each drug, resulting in an overall RR of 1.65 (95% CI, 1.19-2.29; $P=.003$) for the atypical drugs combined and weak trends for increased risks with individual drugs (FIGURE 4).

Although not a planned analysis, data were available from the 2 contrasts with haloperidol from a 12-week risperidone trial[5] and a 10-week quetiapine trial[11,12] and were combined. There were 15 deaths (6.2%) with haloperidol and 9 (3.8%) with placebo among 243 patients receiving haloperidol and 239 patients receiving placebo. Risk for death was calculated as an OR of 1.68 (95% CI, 0.72-3.92; $P=.23$). Using exposure data for haloperidol from the risperidone trial (A. Greenspan, Janssen Pharmaceuticals Inc, written communication, December 7, 2004) and from the quetiapine trial,[11,12] we calculated an RR for haloperidol of 2.07 (95% CI, 0.78-5.51; $P=.15$).[31]

COMMENT

Overall, the use of atypical antipsychotic drugs for relatively brief periods of less than 8 to 12 weeks was associated with a small increased risk for death compared with placebo. The increased risk only could be identified when the

Figure 2. Deaths by Individual Comparisons by Drugs and Overall Compared With Placebo



CI indicates confidence interval; OR, odds ratio.
*Unique identification code which identifies the study or the collection of posters, abstracts, unpublished manuscripts, or published trials of the study drug. The total number of placebo patients is 1757 and deaths, 40. The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.

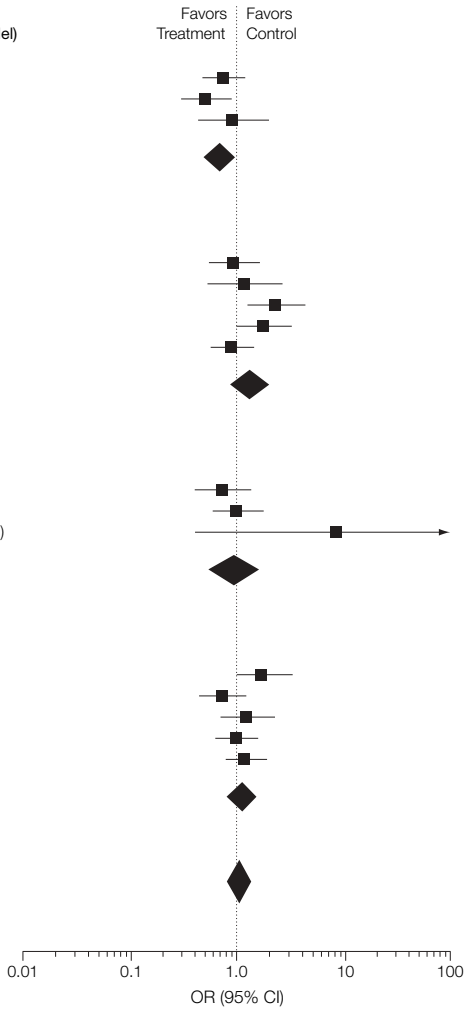
atypical drugs were combined in a meta-analysis. The meta-analyses of each drug were not statistically significant, although the point estimates of the ORs ranged between 1.3 and 1.9. The upper bounds of the CIs, however, ranged from 2.2 to 4.6 and are compatible with the possibility of moderately increased risks. The supplementary analysis of risk rates using time of exposure to drug supported this finding.

A recent FDA public health advisory[27] reporting an increased risk between 1.6 and 1.7 is consistent with our estimates and also mitigates the likelihood of bias or significant errors in our acquisition of the available data. The fact that 12 of the 15 atypical drug comparisons showed more deaths with antipsychotic drug than placebo lessens the possibility that there was bias in the ascertainment and reporting of the deaths in any particular trial. Nevertheless, because any bias no matter how small could be additive to the overall effect, it would have been better if clear unambiguous complete trial reports had been available rather than posters and presentations with partial data that had to be reconstructed. In this respect, it is notable that most of the unpublished trials have been completed for several years and publication is long overdue.

The unpublished trials, however, were of similar quality to the published trials. All were required to be randomized and double-blinded. All but one of the trials were sponsored and conducted by drug manufacturers. The likely reasons for the delays in publication were that most did not show sta-

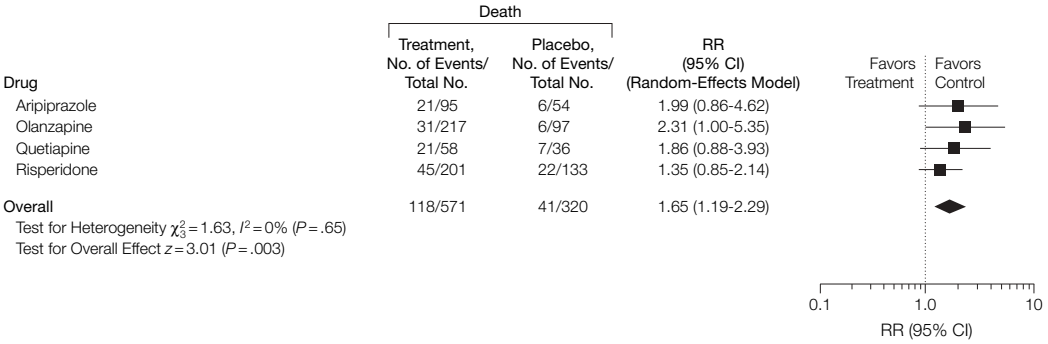
Figure 3. All-Cause Dropouts by Individual Comparisons by Drugs and Overall Compared With Placebo

Source*	All-Cause Dropouts: Treatment, No. of Events/ Total No.	All-Cause Dropouts: Placebo, No. of Events/ Total No.	OR (95% CI) (Random-Effects Model)
Aripiprazole			
CN 138-004[38]	147/366	56/121	0.78 (0.52-1.18)
CN 138-005[39-41]	44/131	61/125	0.53 (0.32-0.88)
CN 138-006[40-42]	18/106	18/102	0.95 (0.47-1.96)
Subtotal	209/603	135/348	0.71 (0.52-0.96)
Test for Heterogeneity $\chi^2_2=2.13$, $I^2=5.9\%$ ($P=.35$)			
Test for Overall Effect $z=2.23$ ($P=.03$)			
Olanzapine			
HGAO[37,43-45]	57/120	57/118	0.97 (0.58-1.61)
HGEU[6,45]	43/159	11/47	1.21 (0.57-2.60)
HGGU[45-47]	77/204	19/94	2.39 (1.34-4.26)
HGIC[45,48]	71/178	24/90	1.82 (1.05-3.18)
HGIV[8,45]	146/523	38/129	0.93 (0.61-1.42)
Subtotal	394/1184	149/478	1.34 (0.92-1.96)
Test for Heterogeneity $\chi^2_4=9.48$, $I^2=57.8\%$ ($P=.05$)			
Test for Overall Effect $z=1.51$ ($P=.13$)			
Quetiapine			
5077 US-039[11,12]	29/124	36/125	0.75 (0.43-1.33)
5077 US-046[49]	86/241	32/92	1.04 (0.63-1.72)
Ballard[33]	3/26	0/29	8.79 (0.43-178.69)
Subtotal	118/391	68/246	0.95 (0.58-1.58)
Test for Heterogeneity $\chi^2_2=2.86$, $I^2=30.1\%$ ($P=.24$)			
Test for Overall Effect $z=0.19$ ($P=.85$)			
Risperidone			
HGGU[45-47]	61/196	19/94	1.78 (0.99-3.21)
RIS-AUS-05[7]	45/167	56/170	0.75 (0.47-1.20)
RIS-INT-24[5,50]	47/115	40/114	1.28 (0.75-2.18)
RIS-USA-232[51]	59/235	59/238	1.02 (0.67-1.54)
RIS-USA-63[4]	146/462	44/163	1.25 (0.84-1.86)
Subtotal	358/1175	218/779	1.14 (0.88-1.47)
Test for Heterogeneity $\chi^2_4=5.95$, $I^2=32.7\%$ ($P=.20$)			
Test for Overall Effect $z=0.97$ ($P=.33$)			
Overall	1079/3353	570/1851	1.07 (0.88-1.30)
Test for Heterogeneity $\chi^2_{15}=30.89$, $I^2=51.4\%$ ($P=.009$)			
Test for Overall Effect $z=0.68$ ($P=.50$)			



CI indicates confidence interval; OR, odds ratio.
*Unique identification code, which identifies the study or the collection of posters, abstracts, unpublished manuscripts, or published trials of the study drug. The total number of placebo patients is 1757 and dropouts, 551. The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.

Figure 4. Deaths Based on Total Drug and Placebo Exposures Pooled by Drug



Total population is patient-years exposure to treatment (drug) or placebo. CI indicates confidence interval; RR, relative risk. Exposure time to treatment for 4 risperidone and 3 olanzapine trials was obtained from data presented by the US Food and Drug Administration.[23] Exposure time for 1 risperidone trial,[46] 2 olanzapine trials,[8,46] and 1 quetiapine trial[33] was estimated from sample sizes, trial lengths, and dropout rates. Exposure time for aripiprazole was calculated from sample sizes and incidence data provided in a letter from Bristol-Myers Squibb (February 10, 2005),[32] and for 2 quetiapine trials from data provided in Schneider et al.[31] The total number of placebo deaths is 40 and placebo exposure is 303 patient-years (see footnote to Figure 2).

tistically significant results on their primary efficacy outcomes, perhaps lessening the enthusiasm of the sponsors to submit the manuscripts. The poster presentations may have represented a compromise in this regard. With respect to death as an outcome, however, a funnel plot of the log ORs against sample size was symmetrical around the mean overall effect, thus not providing evidence for selection bias. Moreover, death and dropout rates did not differ between the 6 published trials (death: OR, 1.42; 95% CI, 0.80-2.51; and dropouts: OR, 1.05; 95% CI, 0.84-1.33) and the 9 unpublished trials (death: OR, 1.63; 95% CI, 1.00-2.65; and dropouts: OR, 1.07; 95% CI, 0.81-1.42).

It can be appreciated that excess mortality could not have been recognized by examining any individual trial. The events were too sparse and the trials too small to be able to meaningfully assess for a dose response that might make attribution even more compelling. Subgroup analyses, limited in statistical power, were unenlightening and did not provide any evidence that risk might differ by drug, psychotic symptoms as criteria for inclusion, living arrangements, or cognitive impairment. Analyses by age, sex, ability to ambulate, or potential interactions could not have been performed unless individual patient data had been available.

It was beyond the potential of our meta-analysis to review each death, although careful investigation of each case is warranted. There is insufficient information available on individual cases, causes or circumstances, baseline clinical characteristics, medical conditions, and concurrent medications. An individual patient meta-analysis might be able to identify characteristics associated with mortality potentially due to drugs. Considering that future trials are unlikely, the pharmaceutical manufacturers, the owners of most of these data, might be encouraged to allow their data to be combined and analyzed by an independent organization without a material interest in the outcomes.

The absolute risk difference of 1% excess deaths (with upper limits to the CI of 4% to 5% depending on the drug), considering that the trials were about 8 to 12 weeks and assuming proportionality in the risk (and that the risk is not just an early effect of treatment), implies a 4% to 5% risk difference over a year of treatment with an upper bound for some drugs as high as 25%. An argument could be made, however, that the risk is highest earlier in treatment with risk diminishing over time. An assumption of no excess deaths over placebo from after the first 3 months of treatment and continuing for a year would effectively decrease the risk estimates above by approximately 25% and result in a similarly markedly lower projected RR for death of 1.15 over the course of a year's treatment compared with the observed RR of 1.65 during the length of the trials. Unfortunately, there is a lack of any long-term controlled studies that can resolve this issue.

Expressing the absolute risk difference as an inverse yields a number needed to harm of 100 with a very broad 95% CI from 53 to 1000, implying that there may be 1 death due to atypical drug use for every 100 patients treated over 10 to 12 weeks. Considering that many of these trials demonstrated that these medications are only modestly effective with numbers needing to treat ranging from 4 to 12 in specific meta-analyses, the likelihood for helping vs harming may be rather modest as well, such that for every 9 to 25 persons helped in these trials there possibly will be 1 death.

Considering the consistency of the risks among the trials, it is likely that there is increased risk from any of the drugs and not from a particular atypical drug. This is supported by the observation that the risk for haloperidol, which was randomly and double-blindedly assigned in 2 of the trials, was similar in magnitude to that of the atypical drugs, although not statistically significant. A fair speculation is that in

frail, often medically ill, elderly patients with dementia a wide range of classes of drugs (antidepressants, sedatives, hypnotics, anxiolytics, mood stabilizers, anticonvulsants, and cardiovascular or antihypertensive drugs) similarly could be associated with this level of risk. This review also demonstrates that there is a substantially larger body of placebo-controlled trials of atypical drugs vs other central nervous system–acting drugs in very elderly patients (>81 years), mainly in an institutionalized population with dementia, and this collection of trials is larger than has previously been identified in the published literature.[9,52]

An absence of evidence for either efficacy or safety with nonatypical antipsychotic drugs was observed and the existing trials are not of adequate statistical power or quality to detect any increased risk at the level reported herein with atypical drugs. It is plausible that increased mortality is associated with the use of many or all classes of drugs used to treat these symptoms and syndromes. In elderly patients, it is likely that any given medication will both help and harm, and the safety of a drug must be considered in the context of known efficacy. Ironically, analyses such as these expose the risks of performing clinical trials in elderly patients as well and are likely to discourage pharmaceutical companies, governments, and institutions from undertaking future trials in this area.

These findings emphasize the need to consider certain changes in some clinical practices. Antipsychotic drugs have been dispensed fairly frequently to patients with dementia and used for long periods. The established risks for cerebrovascular adverse events together with the present observations suggest that antipsychotic drugs should be used with care in these patients. The fact that excess deaths and cerebrovascular adverse events can be observed within 10 to 12 weeks of initiating medication, coupled with observations from individual clinical trials results that there is substantial improvement in both drug and placebo groups during the first 1 to 4 weeks of treatment, lead to the consideration that antipsychotic drugs should be prescribed and dosage adjusted with the expectation of clinical improvement within that time. If improvement is not observed, the medication could be discontinued. 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. Of course, if the risks for serious adverse events are more related to initiation of medication than to continuation, starting and stopping might expose patients to greater risk.

As a meta-analysis, our results should be taken as hypothesis-generating for an increased risk for deaths in patients with dementia receiving atypical antipsychotic drugs. Although the findings were consistent from trial to trial and from drug to drug with no evidence for heterogeneity, they included relatively small numbers of patients and sparse events within any 1 antipsychotic drug. It is only when all trials are combined that a statistically significant effect is found. No drug is individually responsible for the effect, but rather each contributes to the overall effect. This effect may not be limited to atypical drugs as a class and may be associated with haloperidol and other drugs that have not been subjected to efficacy trials in elderly patients with dementia.

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