Chapter 2
Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia: Meta-analysis of Randomized Placebo-Controlled Trials

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Objectives To evaluate the data of increased mortality from atypical antipsychotic drug treatment for older adults with dementia [1].

Methods The authors' search included randomized placebo-controlled clinical trials (RCTs) utilizing MEDLINE (1966 to April 2005) and Cochrane Controlled Trials Register (2005, Issue 1) and non-peer-reviewed documents such as conference

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programs, conference proceedings, abstracts of books, publication abstracts, poster presentations, slides from geriatric medicine, and psychiatric, neurological, and geriatric psychiatric professional society meetings since 1999. Pharmaceutical companies manufacturing atypical antipsychotics were contacted, and information was requested as needed. Search terms used included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, dementia, Alzheimer disease, and clinical trial.

RCTs were eligible for inclusion if they met the following criteria: parallel, double-blind, and placebo-controlled group with random assignment to an orally administered antipsychotic or placebo; the patients were diagnosed with Alzheimer disease, vascular dementia, mixed dementia, or a primary dementia; the numbers were randomized (with obtainable randomization methodology, dropout, and death figures).

The primary outcome assessed was mortality, with a secondary review of dropout rates. The authors included comparisons of several atypical antipsychotic drugs (aripiprazole, olanzapine, quetiapine, and risperidone) given orally and oral placebo. Exclusions were based on not meeting the above criteria and redundant publication. The assessment method formed part of the process by which papers were selected for the review, but the authors did not state who performed the validity assessment.

Additional selection criteria and review processes are not discussed, excepting the delineation between data extraction and confirmation as separate functions performed by distinct reviewers. Data were extracted on all-cause dropouts and deaths occurring within the trial period or 30 days of its conclusion. Dosage groups were aggregated within trials. Odds ratios (ORs) and absolute risk differences were calculated for dropouts and deaths.

Authors combined studies using DerSimonian and Laird random effects model for dropout outcomes and the Mantel-Haenszel fixed-effects model for deaths. A funnel plot analysis assessed potential retrieval bias in comparing published trials with the nonpublished trials (analysis results not included). Outcomes were based on standard assessment methods (with random or fixed-effects models) that calculated ORs, and risk differences included randomized and relative risks for total exposure in patient treatment.

Chi-squared tests and the I-squared statistic examined statistical heterogeneity between studies. Subgroups for sensitivity analyses included patients with diagnosis of psychosis of dementia; outpatients versus nursing home patients; whether mean baseline cognitive severity measured on the Mini-Mental State Examination (MMSE) was less than or equal to 10 or greater than 10; or by drug used.

Results Fifteen trials (9 unpublished), involving a total of 5387 patients, were included in the review. These trials were approximately 10–12 weeks in duration and included 16 comparisons between placebo and the following antipsychotic drugs: aripiprazole ($n = 3$), olanzapine ($n = 5$), quetiapine ($n = 3$), and risperidone ($n = 5$). There were a greater number of deaths in the atypical antipsychotic drug groups compared to the placebo groups (118 versus 40 deaths). The combined OR for all 15 trials by meta-analysis for death in patients treated with antipsychotic

drugs compared with placebo was 1.54 (95% confidence interval (CI), 1.06, 2.23; $P = 0.02$) in favor of placebo, with no significant heterogeneity among the studies. A funnel plot graphing log ORs against sample size did not demonstrate any evidence of selection bias.

The risk differences for death were favorable for placebo than atypical antipsychotic drugs in all trials except three RCTs. Table 2.1 shows risk differences between drugs compared to placebo.

The authors found 1079 all-cause dropouts (32.2%) among the drug-treated groups and 551 (31.4%) among the placebo groups. Table 2.2 shows the risk differences for dropouts in patients treated with atypical antipsychotic drugs compared to placebo. Overall, there were no significant differences in dropouts between the drug and placebo groups, although there was significant heterogeneity among the trials and between drugs ($X^2 = 30.89$, $P = .009$; $I^2 = 51.4\%$). When the risk of death was compared to the risk of dropouts, no association was identified.

Subgroup analyses did not reveal heterogeneity in any of the trials comparing cognitive severity, trials that selected patients with psychosis of Alzheimer disease versus without, or inpatients compared with outpatients or among the four drugs.

In their ad hoc analysis, the authors found that the relative risk of mortality by length of exposure favored placebo when looking at available data on total exposure to drug or placebo in patient-years. An overall relative risk of 1.65 (95% CI, 1.19–2.29; $P = .003$) was calculated for atypical antipsychotics as a group, but weaker trends in risk of mortality were found when analyzing individual drugs.

Conclusions Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. One should compare the risks and benefits when determining whether to start an antipsychotic medication in the setting of dementia.

Table 2.1 Risk differences for death in patients treated with atypical antipsychotics compared to placebo

Drug	Risk difference	Confidence interval (CI)
Aripiprazole	0.01	95% CI, −0.01–0.03; $P = .20$
Olanzapine	0.01	95% CI, −0.00–0.03; $P = .07$
Quetiapine	0.02	95% CI, −0.01–0.05; $P = .22$
Risperidone	0.01	95% CI, −0.01–0.02; $P = .33$

Table 2.2 Risk differences for dropouts in patients treated with atypical antipsychotics compared to placebo

Drug	Risk difference	Confidence interval (CI)
Aripiprazole	−0.07	95% CI, −0.15–0.01; $P = .10$
Olanzapine	0.06	95% CI, −0.02–0.15; $P = .12$
Quetiapine	0.02	95% CI, −0.08–0.11; $P = .73$
Risperidone	0.03	95% CI, −0.03–0.08; $P = .31$

Strengths of the Study

1. The review question and the inclusion criteria were clear.
2. The search was adequate and included unpublished material.
3. The statistical analysis, including meta-analysis, was appropriate, thorough, and well-conducted.
4. A funnel plot graphing log ORs against sample size did not show evidence of selection bias.
5. The inclusion and exclusion material were clear.
6. Authors utilized meta-analysis to study variation of effect across RCTs, overcome the limits of small sample sizes, and examine differences from conflicting data thoroughly.
7. The unpublished RCTs, manuscripts, technical trial reports, posters, letters, and slide-formatted information could be standardized into the meta-analysis.
8. The study sample included only older adults (≥60 years of age).

Limitations of the Study

1. The authors did not elaborate in detail how the papers were selected for the review, or how many reviewers performed the selection.
2. The authors also did not report using methods to minimize bias and error when selecting studies for their review, and the validity assessment inherent in this process, although such methods were employed in the data extraction.
3. Utilization of posters and presentations with partial data which had to be reconstructed may have contributed to bias.
4. They provide little supporting data on which to base extrapolation using short-term data to longer periods from a 1% number of excess deaths at 8–12 weeks to a 4–5% risk difference over 1 year indicating it is probable that this initial risk is primarily expressed during the initial 12-week drug exposure.
5. The mortality events were negligible and the RCTs were not powered to detect a significant dose response.
6. There was insufficient information available on individual cases, causes or circumstances, baseline clinical characteristics, medical conditions, and concurrent medications.
7. They did not look at individual drugs in response to side effects but looked at overall category.
8. Few observational studies have reported that the mortality risk associated with antipsychotic use in the geriatric patients and older adults with dementia may have a dose-dependent effect.
9. Summarizing large amounts of varying information using a single number is a controversial aspect of meta-analysis as it ignores the fact that treatment effects may vary from study to study.
10. Some data presented with incomplete information and required additional information through other data presentations or from sponsors.

Take-Home Points Overall, the use of atypical antipsychotic drugs for relatively brief periods of less than 8–12 weeks was associated with a small increased risk for death compared with placebo. The number needed to harm, using an inverse of the absolute risk difference, proposes that there may be 1 death due to atypical drug use for every 100 patients treated over 10–12 weeks. The increased risk only could be identified when the 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.

Practical Applications of the Take-Home Points Older adult patients are more likely to experience adverse reactions as the result of age-related pharmacodynamic changes, and it is likely that any given medication may have the potential to both benefit and harm the patient. Although atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo, this risk should be reflected within the setting of medical need for the drugs, evidence of efficacy, medical comorbidity, and the efficacy and safety of alternatives.

It has been shown that antipsychotic drugs have been dispensed frequently to patients with dementia and used for long periods [2]. The findings within this meta-analysis emphasize the need to consider changes in clinical practices with an understanding that the established risks for cerebrovascular adverse events together with the present observations suggest that antipsychotic drugs should be used with care in these patients.

Many of these studies demonstrated increased mortality and cerebrovascular adverse events within 10–12 weeks after initiating atypical antipsychotic medication. It was also noted that within the individual clinical trials, there was substantial improvement for both drug and placebo groups within 1–4 weeks, indicating that when antipsychotic medication is prescribed, it is necessary to modify the dose with the understanding that clinical improvement emerges within this time frame. It is also essential to discontinue the medication if there is no improvement within this time frame to decrease the risk of ongoing adverse effects and increased risk of mortality.

Practicing physicians should understand that improvement in an older adult patient may not only be due to medication additions and/or changes but may also be the result of increased nursing support and care within the nursing facility, environmental changes, or changes in medical status. Naturally, starting and stopping an atypical antipsychotic medication might expose patients to greater risk. As the risks of serious adverse events are often related to initiation of medication than to continuation of medication, providers should assess the patient more frequently in this time period.

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