A review on mortality risks associated with antipsychotic use in behavioral and psychologic symptoms of dementia (BPSD)

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Abstract

Introduction: As the population ages, the prevalence rate of behavioral and psychologic symptoms of dementia (BPSD) rises, and there appears to be an increasing need for pharmacologic treatment where nonpharmacologic treatment would not suffice. Most clinicians are well aware of the increased risks of cerebrovascular event and mortality from antipsychotic use in older adults with dementia. Nevertheless, mortality risks reported in various publications still vary considerably and lack consistency to allow direct comparison between individual drugs.

Methods: A literature search was conducted for primary and secondary sources of evidence regarding the mortality risks associated with antipsychotic use in BPSD.

Results: Available evidence suggests that antipsychotics are indeed associated with elevated risks of cerebrovascular adverse events and mortality. There is also evidence suggestive of a varied risk among individual agents, and a dose-response as well as a time-response relationship.

Discussion: This review aims to provide an updated overview of the publications available on mortality data and risks associated with antipsychotic dose and duration of use. Confounders and limitations are discussed to allow clinicians to better make judgment calls on assessing risks and benefits when treating BPSD with an antipsychotic.

Keywords: antipsychotic, death, mortality, dementia, BPSD, elderly

Introduction

Behavioral and psychologic symptoms of dementia (BPSD) is the collective term for a group of noncognitive symptoms experienced in persons with dementia. It encompasses symptoms such as agitation, delusions, hallucinations, wandering, and mood disturbances, and is estimated to affect up to 60% of persons with dementia dwelling in the community2 and 80% of those who are institutionalized.2,3 Unfortunately, the paucity of evidence for an effective yet safe treatment for BPSD in dementia complicates the management of these patients. Although antipsychotics have been widely used to manage BPSD, with trials and meta-analyses suggesting modest benefit from these agents compared with placebo, no such treatment has been approved by the US Food and Drug Administration (FDA) thus far.4-6 In 2003 and 2004, initial warnings were issued by the FDA and the UK Committee on Safety of Medicines after pooled data across randomized controlled trials (RCTs) of certain atypical antipsychotics (mainly olanzapine and risperidone) demonstrated an increased risk of cerebrovascular adverse events.7,8 In April 2005, the FDA mandated a black box warning regarding an increased risk of mortality in elderly
patients treated with atypical antipsychotics for dementia-related psychosis.9 Subsequently, two observational epidemiologic studies suggested that conventional antipsychotics may confer an even higher risk of death compared with atypical agents,26,31 and a further review of the information led the FDA to extend this boxed warning to all antipsychotics in 2008, although methodologic limitations precluded any conclusion that conventional antipsychotics are associated with an increased risk of mortality versus atypical antipsychotics.13 Mortality risks reported in various publications still vary considerably and lack consistency to allow direct comparison between individual antipsychotics. This review aims to provide an updated overview of the publications available on mortality data and risks associated with antipsychotic dose and duration of use. Confounders and limitations will be discussed to allow clinicians to better make judgment calls on assessing risks and benefits when treating BPSD with an antipsychotic.

Methods

Literature searches were conducted through PubMed and Ovid/MEDLINE. Keyword terms searched were dementia, mortality, death, elderly, geriatric, antipsychotics, behavioral and psychologic symptoms of dementia, and BPSD. All searches were limited to humans, published between January 2005 and June 2015, and written in the English language. Some articles, as identified in Tables 1 through 3, that studied the elderly population without a diagnosis of dementia, and were obtained from this literature search, were included to facilitate discussion within this article.

Mortality Data

Findings from internal FDA data in 2005, which reviewed a total of 17 placebo-controlled trials (7 trials for risperidone, 5 for olanzapine, 3 for aripiprazole, and 2 for quetiapine) in the elderly (n = 5106) with BPSD, revealed an approximately 1.6- to 1.7-fold increase in mortality for patients on an atypical antipsychotic compared with placebo. Most deaths were attributed to cardiac-related events, such as heart failure and sudden death, or infections (mainly pneumonia). Based on this information, the FDA concluded that the mortality risk is probably related to the common pharmacologic effects of all atypical antipsychotic medications, including those that have not been studied in the dementia population.9

A meta-analysis performed by Tan et al20 suggested that individually, risperidone was significantly associated with increased incidence of stroke, but this effect was not seen with aripiprazole, olanzapine, or quetiapine. Although the general trend of these studies points to quetiapine as having the lowest risk and haloperidol having the highest mortality risk, a recent review by Hulshof et al21 seems to suggest otherwise. Elderly on conventional antipsychotics did not seem to demonstrate an increased mortality risk. Likewise, when the meta-analysis was repeated using only trials involving haloperidol, the risk difference and risk ratios were not statistically significant. It should be noted, however, that the data were pooled from RCTs in the geriatric population with dementia, delirium, or a high risk of delirium.

Dose Relation

Few observational studies (Table 2) have reported that the mortality risk associated with antipsychotic use in the elderly13-17 and the elderly with dementia19 may have a dose-dependent effect. Wang et al13 reported an increased risk of death with a high-dose conventional antipsychotic.
| Source, y       | Study Design (No.)                                                                 | Antipsychotic                                                                                     | Mortality Risk                                                                                     |
|-----------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Schneider et al, 2005 | Meta-analysis of 15 RCTs involving patients with dementia (3353) on atypical antipsychotic and (1757) on placebo | Compared atypical antipsychotic (aripiprazole, olanzapine, quetiapine, or risperidone) with placebo | Absolute mortality risk increment of 1% (CI = 0.4%-2%) in patients with dementia with approximately 10-12 weeks' usage of an atypical antipsychotic, relative to placebo |
| Wang et al, 2005 | Retrospective cohort study on elderly (22 890)                                       | Atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone; conventional antipsychotics: acetophenazine, chlorpromazine, fluphenazine, haloperidol, mesoridazine, perphenazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, loxapine, molindone, pimozide, and thiothixene | Adjusted HR for the use of any conventional antipsychotic compared with atypical antipsychotic was 1.37 (CI = 1.27-1.49) |
| Gill et al, 2007 | Retrospective cohort study on elderly with dementia; community-dwelling older adults (9100) and long-term care residents (4036) | Compared the use of an atypical antipsychotic (risperidone, olanzapine, quetiapine) with no antipsychotic use | Adjusted HRs for the initiation of atypical antipsychotic versus no antipsychotic use in community-dwelling and long-term care groups were 1.31 (CI = 1.02-1.70) and 1.55 (CI = 1.15-2.07), respectively |
| Community-dwelling older adults (6888) and long-term care residents (7235) | Compared use of a conventional antipsychotic (haloperidol, loxapine, thioridazine, chlorpromazine, and perphenazine) with that of an atypical antipsychotic | Adjusted HRs for the community-dwelling cohort and long-term care cohort were 1.55 (CI = 1.19-2.02) and 1.26 (CI = 1.04-1.53), respectively |
| Rochon et al, 2008 | Retrospective cohort study on elderly with dementia; community-dwelling residents (20 682) | Compared either an atypical (eg, olanzapine, risperidone, and quetiapine) or conventional (eg, haloperidol, loxapine) antipsychotic with no antipsychotic during the 30 days of follow-up | Adjusted ORs to developing any serious adverse event for atypical antipsychotic and conventional antipsychotic were 3.19 (CI = 2.77-3.68) and 3.81 (CI = 3.31-4.39), respectively, relative to no antipsychotic treatment |
| Retrospective cohort study also on nursing home residents (20 559) | | | Adjusted ORs to developing any serious adverse event for atypical antipsychotic and conventional antipsychotic were 1.92 (CI = 1.68-2.12) and 2.38 (CI = 2.08-2.72), respectively, relative to no antipsychotic treatment |
| Kales et al, 2012 | Retrospective cohort study on elderly with dementia (33 604)                        | Compared antipsychotics (risperidone, olanzapine, quetiapine, or haloperidol) and a nonantipsychotic (ie, valproic acid and its derivatives) using risperidone as reference drug during 180 days | RR for haloperidol was 1.54 (CI = 1.38-1.73), risperidone (reference drug), olanzapine 0.99 (CI = 0.89-1.10), valproic acid and its derivatives 0.93 (CI = 0.78-1.06), and quetiapine 0.73 (CI = 0.67-0.80) |
| Huybrechts et al, 2012 | Retrospective cohort study on geriatric nursing home residents (74 445)             | Compared haloperidol, quetiapine, risperidone, aripiprazole, olanzapine, and ziprasidone using risperidone as a comparator | HR for haloperidol was 2.07 (CI = 1.89-2.26), quetiapine 0.81 (CI = 0.75-0.88). No clinically significant differences were observed for aripiprazole, olanzapine, and ziprasidone |
versus a low-dose conventional antipsychotic relative to an atypical antipsychotic. Gerhard et al\textsuperscript{17} found a dose-dependent change in risk of non–cancer-related death for haloperidol, risperidone, and olanzapine, but not with high-dose quetiapine. Additionally, Maust et al\textsuperscript{19} reported that atypical antipsychotics as a group displayed a higher mortality in the high-dose group compared with the low-dose group. The increased mortality risk was not statistically significant for the medium-dose group compared with the low-dose group.

### Duration of Use

As presented in Table 3, most of the studies have reported that an increased risk of death seemed to climb shortly upon antipsychotic initiation, which may change with the continued use of the antipsychotic.\textsuperscript{10,13,15,22} The observed temporal relationship, however, did not appear to be consistent among studies\textsuperscript{23} and ranged from 30 days up until the end of the study duration of 180 days.\textsuperscript{20} Wang et al\textsuperscript{13} reported a higher mortality risk with conventional antipsychotics relative to atypical antipsychotics at all time points studied. Using risperidone as a comparator, Kales et al\textsuperscript{15} found the relative risk of death for haloperidol to be greatest within 30 days of initiation but dropped drastically and was not statistically significant between 90 and 120 days. The risk of death for atypical antipsychotics was greater on average during the first 120 days of use, compared with the period between 120 and 180 days. Interestingly, Kleijer et al\textsuperscript{22} suggested the risk of cerebrovascular adverse events was found to be much higher within 1 week of antipsychotic initiation but

### TABLE 1: Mortality data and risks associated with antipsychotic use (continued)

| Source, y | Study Design (No.) | Antipsychotic | Mortality Risk |
|-----------|--------------------|---------------|----------------|
| Gerhard et al\textsuperscript{17} 2014 | Retrospective cohort study on community-dwelling elderly (136 393) | Compared aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone using risperidone as a comparator | HR of 180-day mortality risk for haloperidol was 1.18 (CI = 1.06-1.33), quetiapine 0.81 (CI = 0.73-0.89), and olanzapine was 0.82 (CI = 0.74-0.90) |
| Tan et al\textsuperscript{20} 2015 | Meta-analysis of 23 RCTs involving the use of atypical antipsychotics in BPSD (5819) | Compared atypical antipsychotic (risperidone, aripiprazole, olanzapine, and quetiapine) as a whole and individually with placebo | OR of stroke risk for atypical antipsychotic usage as a whole was 2.62 (CI = 1.45-4.75). Individually, OR of risperidone was 4.53 (CI = 1.75-11.72). Effect was not seen with aripiprazole, olanzapine, or quetiapine. ORs of mortality risk for both pooled antipsychotic group (1.06 (CI = 0.65-1.73)) and individual antipsychotic were not statistically significant |
| Hulshof et al\textsuperscript{21} 2015 | Systematic review and meta-analysis of 17 RCTs involving elderly with dementia, delirium, or a high risk of delirium (2387) | Compared conventional antipsychotics (haloperidol, trifluoperazine, thiothixene, thioridazine, loxapine, and perphenazine) with placebo | Pooled risk difference was 0.1% (CI = -1.0% to 1.2%) and risk ratio was 1.07 (CI = 0.54-2.13). Meta-analysis was repeated using only trials involving haloperidol (11 trials, n = 1799); the risk difference and risk ratios were 0.4% (CI = -0.9% to 1.6%) and 1.25 (CI = 0.59-2.65), respectively, and not statistically significant |
| Maust et al\textsuperscript{19} 2015 | Retrospective case-control study on elderly with dementia (90 786) | Compared haloperidol, risperidone, olanzapine, quetiapine, antidepressant, and valproic acid and its derivatives with respective matched nonusers during 180 days | Mortality risk increment for haloperidol was 3.8% (CI = 1.0%-6.6%), risperidone 3.7% (CI = 2.2%-5.3%), olanzapine 2.5% (CI = 0.3%-4.7%), quetiapine 2.0% (CI = 0.7%-3.3%), and antidepressant 0.6% (CI = 0.3-0.9), whereas that of valproic acid and its derivatives was not statistically significant |

BPSD = behavioral and psychologic symptoms of dementia; CI = 95% confidence interval; HR = hazard ratio, OR = odds ratio; RCT = randomized controlled trial; RR = relative risk.
decreased to its baseline after 3 months of use. In contrast, Ballard et al.\textsuperscript{23} found mortality rate to rise over time for the group assigned to continue antipsychotic treatment compared with those assigned to switch to a placebo.

**Limitations**

Despite having numerous studies and meta-analyses published on this subject matter, many of the findings still require careful interpretation. Most of the studies were retrospective cohort studies, and data from such cohort studies are observational in nature. The lack of randomization makes it tough to eliminate confounders. The early discontinuation of treatment,\textsuperscript{10,15} presence of terminal illnesses,\textsuperscript{21} unreported causes of death,\textsuperscript{10} and comorbid delirium\textsuperscript{15} likewise contribute to confounding factors in reported trials. Meta-analyses were often limited by underreporting of less common adverse events in the individual trials.\textsuperscript{24,26} Moreover, publication bias may also result in important figures being omitted. The paucity of data on antipsychotics with a lower usage, such as aripiprazole, ziprasidone, and some conventional antipsychotics, makes it difficult to conclude which agents are comparatively safer. Other limitations encountered included unclear baseline differences of the study population, insufficient blinding, and absence of clear details on the methods of blinding.\textsuperscript{21} One meta-analysis included trials that excluded individuals taking psychotropic medications as well as trials that allowed individuals on psychotropics, such as cholinesterase inhibitors and other drugs.\textsuperscript{20} In spite of the progressive nature of the disease, many studies did not account for the severity of dementia and lacked details on the symptoms of behavior or psychiatric illness,\textsuperscript{17,19-21} although analyses suggested a relationship between mortality and some neuropsychiatric symptoms.\textsuperscript{19} In studies using data derived from prescriptions, the presence of occasional as-needed use and varying titration schedules across agents may also contribute to the potential for misclassification.\textsuperscript{27,28} Finally, not all studies reviewed in this manuscript conform to the diagnosis of BPSD, and some studies focused on the elderly population without a diagnosis of dementia.

**Conclusion**

Available data on the safety of antipsychotics in BPSD management suggests that antipsychotics are indeed

| Table 2: Mortality risk associated with antipsychotic dose |
|----------------------------------------------------------|
| **Source, y** | **Study Design (No.)** | **Antipsychotic** | **Mortality Risk** |
| Wang et al,\textsuperscript{13} 2005 | Retrospective cohort study on elderly (22 890) | Atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone | An increased adjusted HR for death risk within 180 days of 1.73 (CI = 1.57-1.90) for high-dose (greater than median) conventional antipsychotic versus 1.14 (CI = 1.04-1.26) for low-dose (lower than median) conventional antipsychotic relative to an atypical antipsychotic |
| Gerhard et al,\textsuperscript{17} 2014 | Retrospective cohort study on community-dwelling elderly (136 393) | Dose ranges used: Low: haloperidol ≤1 mg, risperidone ≤0.5 mg, olanzapine ≤2.5 mg, quetiapine ≤25 mg Medium: haloperidol >1 to 4 mg, risperidone >0.5 to 1 mg, olanzapine >2.5 to 5 mg, quetiapine >25 to 50 mg High: haloperidol >4 mg, risperidone >1 mg, olanzapine >5 mg, quetiapine >50 mg | As a group, the study antipsychotics showed a combined HR of 1.36 (CI = 1.24-1.49) for high-dose and 1.19 (CI = 1.10-1.27) for medium-dose compared with low-dose antipsychotic |
| Maust et al,\textsuperscript{19} 2015 | Retrospective case-control study on elderly with dementia (90 786) | Dose ranges used: Low: risperidone 0.13-1 mg, olanzapine 1.25-3.75 mg, quetiapine 0.75-112.5 mg Medium: risperidone 1.25-2 mg, olanzapine 5-6 mg, quetiapine 125-200 mg High: risperidone 2.5-9 mg, olanzapine 7.5-40 mg, quetiapine 225-1600 mg | Atypical antipsychotics as a group displayed a 3.5% (CI = 0.5%-6.5%) higher mortality in the high-dose group compared with the low-dose group. The increased mortality risk of 1.3% (CI = −0.1% to 2.7%) was not statistically significant for the medium-dose group compared with the low-dose group |

CI = 95% confidence interval; HR = hazard ratio.
associated with elevated risks of cerebrovascular adverse events and mortality. There is also evidence suggestive of the mortality risk varying among individual agents, with haloperidol having a higher risk of mortality compared with risperidone, olanzapine, and quetiapine.\textsuperscript{37-39} Using a high-dose rather than a low-dose atypical antipsychotic (eg, risperidone 3 mg versus 0.5 mg) may be associated with additional mortality.\textsuperscript{19} The risk of death with haloperidol and atypical antipsychotics is greatest within 30 days and up to 120 days of initiation, respectively, and tends to decrease thereafter,\textsuperscript{15} which may be a true reflection of how antipsychotics are used in the community setting. In view of the associated risks, it is prudent to consider the lowest effective dose for the shortest duration, keeping in mind the confounders and limitations discussed above. To help practitioners use antipsychotics safely for BPSD management, the Centers for Medicare and Medicaid Services issued a set of guidelines\textsuperscript{24} to highlight principles in dementia care, such as the timeframe to reassess the need for an antipsychotic agent. It is important to note, however, that these findings are mainly for patients with dementia. Antipsychotics are still indicated in geriatric patients who receive a diagnosis of schizophrenia, bipolar disorder, or other major psychiatric diagnoses.\textsuperscript{25}

### TABLE 3: Mortality risk associated with the antipsychotic duration of use

| Source, y | Study Design (No.) | Antipsychotic | Mortality Risk |
|-----------|--------------------|---------------|---------------|
| Wang et al,\textsuperscript{13} 2005 | Retrospective cohort study on elderly (22 890) | Atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone Conventional antipsychotics: acetylphenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, haloperidol, loxapine, molindone, pimozide, thiothixene | Relative mortality risk peaked at 1.56 (CI = 1.37-1.78) within 40 days of conventional antipsychotic initiation Between 40 and 79 days, RR was 1.37 (CI = 1.19-1.59) From days 80 to 180, RR was 1.27 (CI = 1.14-1.41) |
| Gill et al,\textsuperscript{10} 2007 | Retrospective cohort study on elderly with dementia (27 259) | Compared the use of an atypical antipsychotic with no antipsychotic use, and the use of a conventional antipsychotic with that of an atypical antipsychotic | Statistically significant elevation in mortality risk as early as 30 days upon initiation of an atypical antipsychotic relative to no antipsychotic use in both community-dwelling and long-term care residents. The increased risk persisted until the study was completed at 180 days |
| Ballard et al,\textsuperscript{23} 2009 | Randomized, placebo-controlled study on patients with Alzheimer disease (165) | Continuation of antipsychotic treatment (risperidone, chlorpromazine, haloperidol, thioridazine, and trifluoperazine) compared with those assigned to switch to a placebo over the course of 12 months, with additional follow-up lasting 24 to 54 months | At 12 months, cumulative probability of survival was 70% (CI = 58%-80%) for the antipsychotics group compared with 77% (CI = 64%-85%) for placebo. The difference in survival continued to widen, to 46% (antipsychotic) versus 71% (placebo) at 24 months, and to 30% (antipsychotic) versus 59% (placebo) at 36 months |
| Kleijer et al,\textsuperscript{22} 2009 | Retrospective case-controlled study on community-dwelling elderly (26 157) | Antipsychotic use compared with no antipsychotic use | OR for CVAEs was found to be much higher within 1 week of antipsychotic initiation (OR = 9.9 [CI = 5.7-17.2]) and decreased over time and was comparable to nonusers after 3 months of use (OR = 1.0 [CI = 0.7-1.3]) |
| Kales et al,\textsuperscript{15} 2012 | Retrospective cohort study on elderly with dementia (33 604) | Compared antipsychotics (risperidone, olanzapine, quetiapine, or haloperidol) and a nonantipsychotic (ie, valproic acid and its derivatives) using risperidone as reference drug, during 180 days (a median 60-day exposure to haloperidol versus other medications [111 days or longer]) | Relative risk of death for haloperidol (RR = 2.24, P < .001) greatest within 30 days of initiation For risperidone, olanzapine, and quetiapine, the risk of death was 1.5 times greater on average during the first 120 days of use |

CI = 95% confidence interval; CVAE = cerebrovascular adverse event; OR = odds ratio; RR = relative risk.
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