LITERATURE REVIEW   **Open Access**

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

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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 community[1] 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,[10,11] 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.[12] 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]

Table 1 represents the findings of key publications available on mortality data and risks associated with antipsychotic use. Wang et al[13] presented evidence indicating that conventional antipsychotics are at least as likely to cause an increased risk of death in the elderly compared with atypical antipsychotics. In fact, figures reported pointed to a higher mortality risk with conventional antipsychotics than atypical antipsychotics at all time points studied, regardless of whether dementia was present and whether the patient resided in a nursing facility. Likewise, a study conducted by Gill et al[10] showed that initiation of an atypical antipsychotic was associated with a higher risk of death versus no antipsychotic use, and the initiation of a conventional antipsychotic seemed to demonstrate a marginally higher mortality. A meta-analysis by Schneider et al[14] reported a 1% increase in absolute mortality risk in patients with dementia with the use of an atypical antipsychotic relative to placebo, but a sensitivity analysis performed did not point to individual drugs having different risks. However, Kales et al[15] estimated that individual antipsychotics may be associated with different mortality risks, the highest observed with haloperidol and the lowest with quetiapine, compared with a nonantipsychotic. In line with these findings were those presented by Rochon et al[16] suggesting that the initiation of a conventional antipsychotic may be associated with a higher occurrence of any serious adverse event leading to hospitalization or death, compared with an atypical antipsychotic in community-dwelling and nursing home elderly with dementia. Furthermore, retrospective cohort studies in the elderly[17,18] supported findings that haloperidol had a higher risk of mortality compared with atypical antipsychotics. More recently, Maust et al[19] also observed that individuals receiving haloperidol had the greatest risk of mortality, followed by those receiving risperidone, olanzapine, and quetiapine.

A meta-analysis performed by Tan et al[20] 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 al[21] 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 elderly[13,17] and the elderly with dementia[19] may have a dose-dependent effect. Wang et al[13] reported an increased risk of death with a high-dose conventional antipsychotic

TABLE 1: Mortality data and risks associated with antipsychotic use

Source, y	Study Design (No.)	Antipsychotic	Mortality Risk
Schneider et al,[14] 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,[13] 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,[10] 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,[16] 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 = 1.68-2.21) and 2.38 (CI = 2.08-2.72), respectively, relative to no antipsychotic treatment
Kales et al,[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	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 0.91 (CI = 0.78-1.06), and quetiapine 0.73 (CI = 0.67-0.80)
Huybrechts et al,[18] 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

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

Source, y	Study Design (No.)	Antipsychotic	Mortality Risk
Gerhard et al,[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,[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,[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,[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.

versus a low-dose conventional antipsychotic relative to an atypical antipsychotic. Gerhard et al[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[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.[10,13,15,22] The observed temporal relationship, however, did not appear to be consistent among studies[23] and ranged from 30 days up until the end of the study duration of 180 days.[10] Wang et al[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[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[22] suggested the risk of cerebrovascular adverse events was found to be much higher within 1 week of antipsychotic initiation but

Source, y	Study Design (No.)	Antipsychotic	Mortality Risk
Wang et al,[13] 2005	Retrospective cohort study on elderly (22 890)	Atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone Conventional antipsychotics: acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, haloperidol, loxapine, molindone, pimozide, thiothixene	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,[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 This dose-response relationship was most apparent with haloperidol
Maust et al,[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.

decreased to its baseline after 3 months of use. In contrast, Ballard et al[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,[10,15] presence of terminal illnesses,[21] unreported causes of death,[10] and comorbid delirium[21] likewise contribute to confounding factors in reported trials. Meta-analyses were often limited by underreporting of less common adverse events in the individual trials.[14,20] 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.[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.[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,[17,19-21] although analyses suggested a relationship between mortality and some neuropsychiatric symptoms.[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.[17,18] 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 3: Mortality risk associated with the antipsychotic duration of use

Source, y	Study Design (No.)	Antipsychotic	Mortality Risk
Wang et al,[13] 2005	Retrospective cohort study on elderly (22 890)	Atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone Conventional antipsychotics: acetophenazine, 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,[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,[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,[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,[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.

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.[17-19] 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.[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,[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[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.[25]

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