Management of aggression, agitation, and psychosis in dementia: Focus on atypical antipsychotics

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Abstract

The behavioral and psychological symptoms of dementia (BPSD), such as psychosis, agitation, or aggression have a considerable negative impact on the quality of life of both patients and their caregivers. Multiple studies have demonstrated that atypical antipsychotics are efficacious in the treatment of the aggressive and psychotic symptom clusters, and here we review their use in this indication. Because of the safety concerns associated with the use of atypical antipsychotics in this population, these drugs must be used judiciously. For patients with severe BPSD such as psychosis, agitation, or aggression, for whom there are few options, atypical antipsychotics, particularly risperidone and olanzapine, should be considered.

Key words: dementia, BPSD, atypical antipsychotic

Introduction

Dementia, the progressive decline in function across multiple cognitive domains, affects 5 to 8 percent of people over age 65 and nearly 50 percent over age 85.[1,2] As the world population ages, the prevalence of dementia is expected to increase substantially.[3] Although numerous causes of dementia have been identified, the most common types of dementia are Alzheimer's disease with dementia (accounting for approximately two-thirds of cases), vascular dementia, and Lewy body dementia.[4]

Dementia is costly for patients and their families personally, socially, and economically. Problems include difficulty with daily activities such as planning meals, managing finances, and driving.[2] Caregivers—often spouses—bear the brunt of social and financial hardships. The economic impact of dementia on society is likewise significant, including costs for long-term institutional care, home care, and lost productivity of caregivers.[2] The annual cost of Alzheimer's disease varies by country but is nearly $100 billion in the United States alone.[2] The high prevalence and significant impact of dementia warrant careful evaluation of disabling dementia symptoms and their treatment.

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Behavioral and psychological symptoms of dementia

Although dementia is diagnosed by observing cognitive symptoms, noncognitive abnormalities are also prevalent in dementia and were, in fact, described by Alois Alzheimer in his original description of what would become known as Alzheimer's disease. Behavioral and psychological symptoms of dementia (BPSD) include signs of disturbed perception, thought content, mood, or behavior.[5,6] BPSD tend to occur in clusters, which have been grouped into the categories of aggression, psychomotor agitation, psychosis, apathy, and depression.[7]

BPSD significantly impact quality of life for both patients and their caregivers.[3] Caregivers consistently rate BPSD symptoms as the most stressful aspect of caring for dementia patients.[8] BPSD also result in increased hospitalizations and emergency department visits[1] and are frequently cited as a primary factor in the decision for institutionalization.[9,10] In 1992, an expert panel of the US Alzheimer's Association identified BPSD as a first priority for research.[11] Recognition of the need for targeting BPSD in dementia research has resulted in the

Table 1. Efficacy and tolerability of atypical antipsychotics in BPSD			
Treatment, daily dosage, and duration	**Population (N), type of dementia**	**Efficacy**	**Tolerability**
Risperidone			
Double-blind risperidone (1.1 mg), haloperidol (1.2 mg), or placebo 12 weeks[33]	AD, VaD, or mixed dementia with DPSD and institutionalized (344)	BEHAVE-AD reduced 53 percent with risperidone, 45 percent haloperidol, and 37 percent placebo (risperidone vs. placebo; $p = 0.05$). CMAI reduced 15 percent with risperidone, 12 percent haloperidol, 6 percent placebo (risperidone vs. placebo; $p < 0.05$)	Somnolence in 18 percent with haloperidol, 12 percent risperidone, 4 percent placebo. EPS in 22 percent with haloperidol, 15 percent risperidone, 11 percent placebo
Double-blind risperidone (0.5 – 2 mg) or placebo 12 weeks[32]	AD, VaD, or mixed dementia with DPSD and institutionalized (625)	BEHAVE-AD aggressiveness decreased 37 percent with 1 mg risperidone and 47 percent with 2 mg ($p < 0.01$). CMAI aggression scales significantly decreased with 1 and 2 mg risperidone ($p < 0.01$). CGI reduced 21 percent with 1 mg and 24 percent with 2 mg ($p < 0.01$)	Risperidone groups showed dose-dependent somnolence (10 – 28 percent vs. 8 percent with placebo) and EPS (7 – 21 percent vs. 7 percent with placebo)
Double-blind risperidone (0.8 mg) or haloperidol (0.9 mg) 12 weeks[34]	AD, VaD, or mixed dementia with DPSD and institutionalized (58)	BEHAVE-AD aggressiveness decreased 1.3 with both drugs; CMAI decreased 8.1 with risperidone vs. 10.0 haloperidol	Signficant increased in EPS with haloperidol ($p < 0.001$); no increase with risperidone.
Double-blind risperidone (0.95 mg) or placebo 12 weeks[35]	AD, VaD, or mixed dementia with DPSD and institutionalized (337)	BEHAVE-AD reduction significantly better with risperidone (36 percent) vs. placebo (12 percent; $p < 0.001$); CMAI decreased 23 percent more with risperidone than placebo ($p < 0.001$)	Somnolence in 26 percent risperidone vs. 25 percent placebo; EPS is 6 percent with risperidone vs. 3 percent placebo
Double-blind risperidone-haloperidol crossover study eight weeks for each medication[36]	AD, VaD, or mixed dementia with DPSD and institutionalized (120)	Improvement in total BEHAVE-AD and CMAI scores was greater with risperidone than haloperidol ($p < 0.005$)	Significant increase in EPS with haloperidol but not risperidone
Olanzapine			
Double-blind olanzapine (5 – 15 mg) or placebo 6 weeks[38]	AD with BPSD (206)	BPRS improved 13 – 22 percent with olanzapine vs. 5 percent placebo (5 mg, $p < 0.01$); NPI improved 35 – 53 percent with olanzapine vs. 25 percent placebo (5 and 10 mg, $p < 0.01$)	Somnolence higher with olanzapine (25 – 36 percent vs. 6 percent); EPS similar for olanzapine and placebo
Double-blind olanzapine (5 – 15 mg) or placebo 6 weeks[40]	AD with BPSD without psychosis (165)	Increase in NPI-psychosis was more likely to occur in patients taking placebo ($p = 0.006$)	Somnolence higher with olanzapine (33 – 40 percent vs. 9 percent); Higher incidence for olanzapine and placebo
Double-blond olanzapine (1 – 7.5 mg) or placebo 10 weeks[39]	AD with psychosis (652)	BPRS significantly improved with olanzapine 7.5 mg (37 percent) vs. placebo (26 percent; $p < 0.05$); No significant difference for NPI-psychosis or CGI-change	Higher incidence of increased weight, anorexia, and urinary incontinence with olanzapine

Table 1. Efficacy and tolerability of atypical antipsychotics in BPSD (continued)			
Treatment, daily dosage, and duration	**Population (N), type of dementia**	**Efficacy**	**Tolerability**
Other			
Double-blind quetiapine (97 mg), haloperidol (1.9 mg), or placebo 10 weeks[42]	AD with psychosis (284)	Superior improvement in BPRS agitation with quetiapine and haloperidol; Superior functional status with quetiapine	Not reported
Double-blind aripiprazole (10 mg) or placebo 10 weeks[47]	AD with psychosis (208)	Superior improvement in BPRS psychosis subscale with aripiprazole (-1.93 aripiprazole vs. -1.27 placebo, p = 0.03); BPRS total and NPI psychosis were similar between treatments	Mild somnolence in 8 percent aripiprazole vs. 1 percent placebo
AD, Alzheimer's disease; VaD, vascular dementia; mixed dementia, combination of AD and VaD; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS, Brief Psychiatric Rating Scale; BPSD, behavioral and psychological symptoms of dementia; CGI, Clinical Global Impression; CMAI, Cohen-Mansfield Agitation Inventory; EPS, extrapyramidal symptoms; NPI, Neuropsychiatric Inventory.			

development of assessment tools, investigations into treatment strategies, and publications of scientific findings.

This review focuses on the treatment of BPSD, particularly on the aggressive, agitated, and psychotic clusters, as these are primary target symptoms for antipsychotics. Furthermore, the focus is on treatments whose use is supported by the results of randomized controlled clinical trials, particularly the atypical antipsychotics.

Assessment of BPSD

The assessment of BPSD is challenging, due to the natural fluctuations in behavioral symptoms and to the difficulty patients may have in communicating these symptoms.[12] Despite these impediments, a number of sensitive, valid, and reliable scales have been developed for BPSD.[13] The most common scales used in clinical trials are the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[14] the Cohen-Mansfield Agitation Inventory (CMAI),[15] and the Neuropsychiatric Inventory (NPI).[5] These scales generally rely on caregivers' reports or clinical observation of the patient's symptoms but differ in the specific behaviors measured and the psychological symptoms included. For example, the CMAI specifically focuses on agitation and aggression, whereas the NPI and BEHAVE-AD cover a much wider range of symptoms. Studies examining treatments for BPSD should ideally also include an assessment of cognitive function to ascertain whether cognition is affected.[12] Two scales that assess general symptoms, the Clinical Global Impression (CGI)[16] scale and the Brief Psychiatric Rating Scale (BPRS),[17] are also frequently used in evaluations of treatment outcome for BPSD. The CGI is used to obtain physicians' global clinical judgments. Subscales denote disease severity, change of disease conditions, and efficacy.[16] Unfortunately, none of these assessment tools has become the standard for clinical trials, making cross-study comparisons difficult.

Methods

For this review, MEDLINE and EMBASE databases were searched for clinical trials in English, using the search terms psychosis, dementia, and elderly in combination with the names of various drugs. Abstracts of papers derived from these searches were examined to find trials in patients with dementia, which were designed to measure behavioral and psychological endpoints. When large controlled studies were available, retrospective studies, small pilot studies, and open-label studies were not considered.

Treatment options for BPSD

Treatment of BPSD can improve the quality of life for patients and caregivers and reduce patient suffering.[6,18] Nonpharmacological therapies, including patient and caregiver education, behavior management, environmental modifications, sensory interventions using sound and light, and social interaction groups, are largely aimed at addressing patient needs and providing a comfortable and stimulating environment.[6] Thus, it is reasonable to provide these therapies before and in addition to pharmacotherapy.[4,18] When behavioral treatments alone cannot control disabling BPSD, medications are added.

The pharmacological treatments for BPSD that have

been tested in clinical trials include antipsychotics, cholinesterase inhibitors, anticonvulsants (e.g., carbamazepine), antidepressants (e.g., fluoxetine), and memantine, as well as the benzodiazepine lorazepam.[4,18,19] Of these, the anticonvulsants, antidepressants, and lorazepam have little or no positive data to support their use as treatments for BPSD.[19] The cholinesterase inhibitors donezepil and galantamine, as well as memantine, have been shown to have efficacy in the treatment of BPSD, in addition to their effect on cognition. Several controlled trials have found that treatment of patients with Alzheimer's disease with donepezil[20-24] or galantamine[24-27] results in small improvements in behavioral symptoms.

Conventional antipsychotics

Traditionally, conventional antipsychotics were often used for the management of BPSD, and at least 35 trials of varying quality have investigated their efficacy and safety in this condition.[18] A meta-analysis of seven controlled trials of conventional antipsychotics in agitated dementia patients showed modest efficacy, with haloperidol and thioridazine producing benefits in 18 percent more patients than placebo.[28] A more recent Cochrane review of haloperidol for the treatment of agitation in patients with dementia found that aggression was reduced, but there were no improvements in agitation, behavioral symptoms as a whole, or in clinical global impression.[29] Because tolerability is frequently reduced in the elderly and doses of conventional antipsychotics that are high enough to produce efficacy are associated with side effects such as parkinsonism, somnolence, tardive dyskinesia, and falls,[29] the modest benefit of haloperidol treatment may not always be justified.

Atypical antipsychotics

One of the primary advantages of atypical antipsychotics over conventional antipsychotics for the treatment of BPSD, as well as other disorders, is their greater tolerability. These drugs are associated with fewer extrapyramidal symptoms (EPS) than conventional antipsychotics, which is especially important in the elderly due to their increased susceptibility to such reactions.[30] Effective dosages of atypicals in BPSD are generally lower than for schizophrenia, which is another factor that improves tolerability.[31]

Risperidone was the first atypical antipsychotic shown to be effective in treating BPSD and is presently the only atypical antipsychotic that is approved for the treatment of BPSD in a number of countries. Several controlled double-blind studies have demonstrated the efficacy and tolerability of low doses of risperidone in patients with BPSD[32-36] (Table 1). A pooled analysis[37] of three placebo-controlled studies resulted in a sample size large enough (1191 patients) to allow better estimates of effect size, especially in subpopulations. The patients in all three trials were aged 55 years or older, lived in an institution, and had been diagnosed using DSM-IV criteria with dementia of the Alzheimer's type, vascular dementia, or mixed dementia. At baseline, the median Mini-Mental State Examination (MMSE) score was 6 (range, 0 to 23) showing that overall the patients tended to have moderate-to-severe cognitive decline. Patients in two of the trials had a wide range of BPSD, while the third trial focused specifically on patients with aggressive behavior. Two studies used flexible dosing up to 1 or 2 mg twice daily. The third study used randomized fixed doses of 0.5, 1.0, or 2.0 mg/d. In this pooled analysis, risperidone was efficacious at all time points on all the outcome measures (CMAI total and subscales and BEHAVE-AD total and psychotic symptom scales). The positive effects were confirmed by significant improvements in CGI-Severity (CGI-S) and CGI-Change (CGI-C) scales. In general, risperidone showed efficacy regardless of the type or severity of dementia, the presence of psychosis, or the presence of somnolence as adverse event. In studies comparing risperidone with haloperidol, risperidone was at least as effective in improving BPSD overall.[33,34] In a head-to-head crossover trial, risperidone was superior to haloperidol in the treatment of BPSD.[36]

Two double-blind studies have tested the effect of olanzapine on BPSD in patients with dementia[38,39] (Table 1). The first, a six-week study of institutionalized patients with Alzheimer's disease and psychotic or behavioral symptoms, found that olanzapine in doses of 5 or 10 mg/d resulted in significant improvements in the Core Total of the NPI. Furthermore, a post hoc analysis of these patients found a significant attenuation in the emergence of psychosis over the short term compared with placebo[40] (Table 1). Although the duration of this study was only six weeks, the percentage of patients treated with olanzapine who developed psychosis over this period was less than one-third that of placebo. In the second double-blind study, patients with Alzheimer's disease and delusions or hallucinations were randomized to placebo or fixed doses of olanzapine (1.0, 2.5, 5.0, or 7.5 mg/d) for 10 weeks.[39] Treatment with the highest dose resulted in significant decreases in psychosis and overall behavioral disturbances as measured by the NPI/Nursing Home Psychosis Total score and the BPRS. Comparative studies evaluating efficacy with olanzapine and conventional antipsychotics in BPSD are lacking.

Three additional atypical antipsychotics have been studied in BPSD. Zotepine has been studied in one 24-patient open-label trial. Half of the patients had

Alzheimer's disease, and the rest had other forms of dementia. Effects on behavior were similar to the effects of other atypical antipsychotics.[41] Two short, open-label pilot studies with quetiapine in Alzheimer's disease patients found improvements in behavioral symptoms without significant adverse events.[42,43] A larger short-term, open-label study in 151 psychotic elderly patients demonstrated good tolerability as well as improvement in psychotic symptoms and clinical global impressions.[44] A 52-week open-label study in 184 elderly patients with psychotic disorders (72 percent due to general medical conditions such as Alzheimer's disease) found significant improvements in psychotic symptoms and CGI.[45] However, a double-blind placebo-controlled study of quetiapine or rivastigmine in 93 Alzheimer's disease patients with dementia and agitation found no improvement in agitation for either medication and a cognitive decline associated with quetiapine.[46] Recently, the efficacy of aripiprazole was evaluated in patients with psychosis related to Alzheimer's disease. This double-blind placebo-controlled trial showed no difference between aripiprazole and placebo on the NPI psychosis subscale, but on the BPRS Psychosis and BPRS Core subscales aripiprazole showed significantly greater improvements from baseline[47] (Table 1). No published data are currently available for clozapine, ziprasidone, or amisulpride in the treatment of BPSD in elderly patients.

Limited data are available on the use of atypical antipsychotics as a treatment for BPSD in patients with dementia with Lewy bodies.[48] These patients are quite sensitive to developing extrapyramidal symptoms (EPS) when treated with antipsychotics. About half of patients with dementia with Lewy bodies may also develop neuroleptic sensitivity reactions, a life-threatening condition, when treated with D2 receptor antagonists, particularly conventional antipsychotics. The risk is lower with atypical antipsychotics, but cases of neuroleptic sensitivity reactions associated with atypical antipsychotics have been documented. Small open-label studies suggest that quetiapine, with its low affinity for D2 receptors and limited EPS, appears to have a positive effect on psychosis, agitation, and anxiety and may be the preferred atypical antipsychotics for this patient population.[48] Somnolence and orthostasis are common but tend to dissipate after the first week of treatment.[45]

Comparisons of atypical antipsychotics for the treatment of BPSD

Few head-to-head studies have compared the various atypical antipsychotics for the treatment of BPSD.[49-51] In a six-week study,[49] patients with probable Alzheimer's disease, vascular dementia, or mixed dementia were randomly assigned to treatment with risperidone or olanzapine. Improvements from baseline measured by NPI scores were found for both treatment groups, with no between-group differences. In another study,[50] patients with DSM-IV diagnoses of Alzheimer's disease, vascular dementia, or mixed dementia, with NPI scores of 24 or more, were randomly assigned to risperidone, olanzapine, or promazine treatment for eight weeks. Both risperidone and olanzapine were found to be at least as efficacious as promazine in the treatment of BPSD. In a third small double-blind parallel study, 39 agitated, long-term-care dementia patients received acute olanzapine or risperidone.[51] Both drugs significantly reduced CGI and NPI scores, with no significant difference between drugs. The Clinical Antipsychotic Trials of Intervention Effectiveness Alzheimer's Disease Trial (CATIE) is a 36-week study comparing olanzapine, quetiapine, and risperidone.[52] This well-designed and documented trial will hopefully provide valuable data on the comparative clinical profiles of these drugs in BPSD that may assist in treatment selection.

Atypical antipsychotics and safety concerns

The atypical antipsychotics are preferred to the conventional antipsychotics because of their milder side-effect profile, but adverse events associated with their use in elderly patients with dementia are still substantial. Among the 1,191 patients in the risperidone pooled analysis,[37] 84 percent experienced adverse events, the most common being injury, falls, somnolence, EPS-related events, urinary tract infection, purpura, and peripheral edema. Of these, only somnolence, total EPS-related events, and peripheral edema differed from placebo, and there was a trend toward more of these adverse events at the highest risperidone dose (1.5 mg/d or more). Studies with olanzapine have found treatment-related somnolence, gait disturbances, weight gain, anorexia, and urinary incontinence.[38,39]

A landmark two-year study[53] finding cognitive decline in patients with dementia treated with conventional antipsychotics has led to concerns that similar results may be found in patients treated with atypical antipsychotics. Such a relationship was confirmed recently in a study of quetiapine treatment of Alzheimer's disease patients with dementia and agitation.[46] In this study, cognitive decline was measured using the Severe Impairment Battery, a scale developed to quantify cognitive change in patients with severe dementia.[54] Studies with other atypical antipsychotics[32,33,35] that have reported no changes observed in cognitive function have typically measured cognitive changes using the MMSE. Further study will be necessary to resolve this issue.

The most serious safety concern is the recent determination that the use of atypical antipsychotics in patients with dementia is associated with a 1.6- to 1.7-fold increase in mortality. The US Food and Drug Administration (FDA) based this finding on an analysis of 17 clinical trials. Fifteen of the trials showed this numerical increase in mortality. Most of the deaths were due to infections or cardiovascular events. Because this increase is thought to be a class effect, the FDA issued a public health advisory and asked the manufacturers of all of the atypical antipsychotics to include a warning in their labeling.[55,56] The risk for increased mortality was also found for haloperidol, indicating that it is not limited to atypical antipsychotics only.[56] Another concern is the increased risk of cerebrovascular adverse events in elderly patients with dementia associated with atypical antipsychotics, including risperidone, olanzapine, and aripirazole.[57-59] However, further research is necessary to evaluate the association between atypical antipsychotics and cerebrovascular events.[60]

Clinical implications

In the light of these serious risks, atypical antipsychotics must be used with extreme caution in patients with BPSD. They should be targeted toward the treatment of those patients in whom BPSD such as psychosis, agitation, and aggression are prominent and associated with significant distress, functional impairment, or danger to the patient.

Before turning to atypical antipsychotics, other methods of reducing symptoms should be considered. Medical conditions such as untreated pain or depression should be addressed, and nonpharmacological therapies and environmental modifications should be attempted. Medications should be reviewed; some may have neuropsychiatric side effects. For example, treatments for hypertension are common in an elderly population. Medications for hypertension may cause electrolyte imbalances, particularly in the elderly, resulting in symptoms such as confusion or hallucinations. Other medications for dementia, cholinesterase inhibitors and/or memantine, may be prescribed before resorting to atypical antipsychotics. These medications can delay the progression of dementia and postpone the onset of BPSD symptoms, as well as reducing current symptoms. When used in conjunction with an antipsychotic, they may have a dose-sparing effect.[61] Although there are little data on the concomitant use of cholinesterase inhibitors and antipsychotics, safety studies have been published on the use of risperidone with donepezil, galantamine, and rivastigmine.[62-64] Before prescribing atypical antipsychotics, physicians should note risk factors for stroke and cardiovascular disease and regularly monitor patients. Initial doses of atypical antipsychotics should be low and gradually increased. Furthermore, because BPSD tend to be episodic, the need for continuing pharmacological treatment should be reassessed on a regular basis.

Conclusion

Dementia is a devastating illness whose prevalence is increasing as the population ages. BPSD are now widely recognized as contributing significantly to the burden for both patients and caregivers, particularly since no treatment yet exists to reverse the neuronal degeneration that characterizes dementia. Double-blind placebo-controlled trials have demonstrated that atypical antipsychotics, particularly risperidone and olanzapine, cause modest improvements in BPSD, particularly in agitation, aggression, and psychosis, but even modest improvement can have a great impact on patient and caregiver quality of life.

Because of the increased risk of mortality associated with the use of atypical antipsychotics in elderly patients with dementia, they should be used in patients whose symptoms cause significant morbidity, patient suffering, and the potential for harm to self. The decision to use atypical antipsychotics should be based on the individual's medical history and circumstances, the potential benefits of treatment, and the overall treatment risks.

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For best consideration, letters pertaining to a specific issue should be received as soon after publication as possible. All letters should be typewritten and double-spaced; references should be limited to five when possible.

Please include your full name, position, and address. Mail correspondence to the following address:

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