

Antipsychotic use in elderly patients with dementia: Efficacy and safety concerns

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ABSTRACT

Behavioral and psychiatric symptoms of dementia (BPSD) refer to a heterogeneous group of symptoms that represent non-cognitive complications of Alzheimer's disease (AD) and other dementias. Currently, there are no FDA-approved antipsychotic medications for management of BPSD in the United States. Second generation antipsychotics (SGAs) should only be used for appropriate and justified BPSD targets including distressing and severe physical aggression and/or disturbing hallucinations or delusions that pose a risk of harm to self or others after non-pharmacologic interventions have failed. At best, SGAs provide only modest effects and are associated with increased risk for mortality and cerebrovascular complications in addition to other agent-specific side effects. Current evidence and recommendations support use of risperidone, aripiprazole or olanzapine for Alzheimer's disease (AD) and vascular dementia (VaD), and use of quetiapine or clozapine for Lewy body dementia (LBD) and Parkinson's disease dementia (PDD). Any SGA should be initiated at low dosages with slow titration; and the lowest effective dose should be used as a maintenance dose only for a short period of time. Patients should be monitored for clinical response and adverse effects and should be periodically evaluated for continued need for medication. Appropriate use of SGAs for management of BPSD is critical to increase safety for our growing elderly population with dementia.

INTRODUCTION

Behavioral and psychiatric symptoms of dementia (BPSD) also known as neuropsychiatric symptoms (NPS) represent a heterogeneous group of psychiatric, psychological and mood disturbances or behaviors such as aggression, agitation, psychosis (hallucinations, delusions), wandering, repetitive speech, depression, anxiety, apathy and sleep disturbances, among others.¹⁻² BPSD are common non-cognitive clinical features of dementias of different etiologies such as Alzheimer's disease (AD), Parkinson's disease dementia (PDD), Lewy body dementia (LBD) and vascular dementia (VaD).³⁻⁴ Symptoms and their frequency can vary among different types of dementia as well as among the different stages of dementia. In general, BPSD are more commonly reported in those with a more advanced stage of the disease.^{1,5-6} Due to the fact that patients with more advanced dementia are usually institutionalized, it is not surprising that over 80 percent of residents living in nursing homes were reported to experience one or more BPSD⁶ while only about 60 percent of similar community-

dwelling residents experienced one or more BPSD.¹ Affective symptoms such as depression or anxiety are common during mild stages while delusions, hallucinations (mainly visual), and aggression are more common in moderate to severe stages.⁵ BPSD symptoms, specifically psychosis and physical aggression, can have a significant impact on a patient as well as his/her family's and caregivers' quality of life.⁷⁻⁹ BPSD, especially in later dementia stages, are associated with increased caregiver distress leading to increased caregiver burden and early nursing home placement.¹⁰⁻¹⁴

The efforts to manage behavioral and psychiatric disturbances in dementia involve non-pharmacologic approaches^{5,15-16} and pharmacologic treatments.^{2,5,15,17} The main goal of these strategies should be improving or maintaining quality of life for a dementia patient. For dementia patients, antipsychotic medications, mainly second generation antipsychotics (SGAs), are often clinically prescribed off-label for management of BPSD.^{1-2,18} Importantly, the majority of patients suffering from AD and other common dementias are elderly patients.

The largest number of all antipsychotic prescriptions prescribed for elderly patients were reported to be those for BPSD.¹⁹ Given the scientific evidence and recommendations, what is proper place in therapy for antipsychotics in elderly dementia patients?

EFFICACY CONCERNS OF ANTIPSYCHOTIC USE FOR BPSD SYMPTOMS IN ELDERLY WITH DEMENTIA

The most frequently studied SGA agents in dementia populations, especially those with AD and VaD, are risperidone, olanzapine, quetiapine and aripiprazole. Clinical trials assessing the efficacy of SGAs compared to placebo for dementia-related aggression, agitation or psychosis have been limited and have yielded mixed results.^{17,20-26} In general, these antipsychotics trials were typically of short duration (6-12 weeks), heterogeneous with regard to clinical setting, patient population, type and severity of dementia, BPSD symptoms, and assessments for severity and symptom improvement.

A meta-analysis of 15 RCTs (n=3,353) assessed effectiveness of SGAs, aripiprazole, quetiapine, olanzapine and risperidone, for dementia-related agitation and or/psychosis, with 11 trials in nursing homes and four in outpatient care settings. The vast majority of studies' participants were institutionalized elderly women (mean age=81 years) with AD. Small but statistically-significant improvement in psychosis scores with risperidone were identified whereas the global neuropsychiatric disturbance was improved with aripiprazole and risperidone groups without such associations for olanzapine and quetiapine in institutionalized females with AD.²⁷ The largest multicenter, outpatient, placebo-controlled trial, Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer Disease (CATIE-AD)²⁴ included 421 patients with AD and agitation, aggression or psychosis. Patients were randomized into several treatment groups and received treatment with a flexible-dose of olanzapine (mean dose=5.5 mg/day), risperidone (mean dose=1.0 mg/day), quetiapine (mean dose=56.5 mg/day), or placebo for up to 36 weeks. With regard to time to discontinuation for any reason, treatment with risperidone (median=7.4 weeks), olanzapine (median=8.1 weeks), and quetiapine (median=5.3 weeks) were no different (P=0.52) than placebo (median=8.0 weeks). There was no difference between antipsychotic-treated and placebo groups in the number of patients with at least minimal improvement on the clinical global impression of change (CGIC) at 12 weeks. The time to discontinuation due to efficacy favored olanzapine (mean=22.1 weeks) and risperidone (mean=26.7 weeks)

as compared to quetiapine or placebo (P=0.002), but this seemed to be offset by shorter time to discontinuation due to adverse effects in the antipsychotic groups: olanzapine (24%), risperidone (18%), quetiapine (16%), and placebo (5%). On the other hand, the analysis of individual symptoms from the CATIE-AD trial²⁸ revealed that treatment groups receiving olanzapine or risperidone showed significantly greater improvement on the Neuropsychiatric Inventory (NPI) total score compared to those randomized to quetiapine or placebo groups. Those in the risperidone group showed significant improvement on the Clinical Global Impression of Change (CGI-C) measure. In addition, on the Brief Psychiatric Rating Scale (BPRS), in comparison with placebo, the hostility-suspiciousness factor improved with olanzapine and risperidone, whereas the psychosis factor improved significantly only with risperidone. There were no differences between SGAs and placebo on measures of cognition, activities of daily living (ADL) or quality of life. Of note, functional decline was observed in the olanzapine-treated when compared to the placebo-treated group. Recently, Maglione et al.²⁹ performed a meta-analysis of 37 RCTs (n=5,364) to examine off-label use of SGAs. Pooled results from 17 RCTs showed statistically-significant but clinically modest effects of olanzapine, risperidone or aripiprazole compared to placebo for agitation or psychosis in elderly patients with dementia. The standard mean difference was 0.22 (95%CI=0.09-0.35). Risperidone had the best evidence of efficacy for psychosis while risperidone and olanzapine had the best evidence of efficacy for agitation.²⁹

Not all antipsychotic trials in dementia patients yielded favorable results. For example, a 26-week randomized double-blind controlled trial²³ with fixed-dose of quetiapine (100 mg/day) and rivastigimine (9-12 mg/day) in institutionalized AD patients (n=93), most with severe dementia (functional assessment staging scores >5), found no significant differences between treatments in the change in agitation inventory scores between baseline and six or 26 weeks. In addition, at six weeks, compared to baseline, the quetiapine-treated group experienced significantly greater dysfunction on a severe impairment battery compared to placebo-treated patients, with an estimated mean difference in change in severe impairment battery score of -14.6 points compared with the placebo treated group (95%CI=-25.3 to -4.0; P = 0.009).²³

In summary, antipsychotics may be more effective and can be appropriate treatment targets for antipsychotics under certain circumstances for particular symptoms (i.e.,

psychosis, hallucinations and/or delusions) and some forms of agitation such as physical aggression^{15,30-33} but not for insomnia, pacing or other stereotypical behaviors, social withdrawal, wandering, verbal aggression, apathy or depression. Controlled trials of SGA efficacy for dementia patients with psychosis and agitated or aggressive behavior are limited showing, at best, a modest effect compared to placebo, although studies have not always found significant advantage over placebo in terms of psychotic symptoms. Based on the current (albeit limited) evidence, it seems that risperidone, aripiprazole, olanzapine and, to some degree, quetiapine are the most efficacious for reduction of selected BPSD symptoms in AD and possibly VaD.²⁹

SAFETY CONCERNS OF ANTIPSYCHOTIC USE FOR BPSD SYMPTOMS IN ELDERLY WITH DEMENTIA

In general, elderly patients are more sensitive to antipsychotic-induced adverse effects at least in part due to pharmacokinetic and pharmacodynamic changes resulting from the normal aging process.³⁴⁻³⁵ Elderly patients also tend to have more comorbidities and, as a result, may take more medications which increases their risk for drug interactions. Common SGAs-associated adverse effects (Table 1) such as sedation, orthostatic hypotension, metabolic and anticholinergic adverse effects can lead to an increased risk for falls, cognitive impairment, morbidity and decreased quality of life among elderly patients with dementia.

The CATIE-AD trial with aripiprazole, risperidone, quetiapine and olanzapine reported that time to discontinuation due to tolerability favored placebo over SGAs (P=0.009). There were high rates of parkinsonism or extrapyramidal symptoms in olanzapine (12%) and

risperidone (12%) groups compared to quetiapine (2%) or placebo (1%).²⁴ A Canadian retrospective cohort study⁴³ of all adults 66 years and older (n=25,769) in Ontario identified 449 events of parkinsonism among older adults prescribed antipsychotics (11,573 person-years). Relative to individuals dispensed an atypical antipsychotic, the likelihood of development of parkinsonism was higher for those dispensed a typical agent (HR=1.30; 95%CI=1.04-1.58) and lower for those not exposed to any agent (HR: 0.40; 95% CI: 0.29-0.43). Furthermore, compared to those dispensed a high-dose atypical antipsychotic, those dispensed a typical antipsychotic were at similar risk for parkinsonism (P=0.7). Among atypical antipsychotics, quetiapine and clozapine are associated with the lowest risk for extrapyramidal symptoms (EPS)⁴⁴⁻⁴⁵ and therefore are most appropriate for use in patients with PDD and LBD. LBD patients have been reported to have marked sensitivity, including life-threatening neuroleptic malignant syndrome, to typical and atypical antipsychotics⁴⁶⁻⁴⁷, thus antipsychotics should only be used if other strategies have failed to control severe psychosis and/or agitated/aggressive behavior. It has been reported that a CNS cholinergic deficit might be more pronounced in LBD patients compared to AD and other related dementias. This may make cholinesterase inhibitors a mainstay in the treatment of cognitive problems, as well as for reduction of psychosis and other neuropsychiatric disturbances in LBD patients.⁴⁸

In the general population, clozapine and olanzapine represent the highest offenders causing metabolic disturbances while risperidone and quetiapine are associated with moderate risk and aripiprazole with the most favorable metabolic profile^{36,49-50} (Table 1). The

Table 1. Adverse Effects Associated with Most Commonly Used SGAs for Management of BPSD in Dementia Patients^{33,36-42}

SGA	Sedation	Ach AEs	EPS	Orthostatic Hypotension	Metabolic Disturbances	Other
aripiprazole	low	vlow	low	vlow	low	hiccups akathisia QTC prolongation
clozapine	high	high	vlow	high	high	agranulocytosis seizure siallorhea tachycardia hyperthermia QTC prolongation
olanzapine	high	mod	low	mod	high	QTC prolongation
risperidone	low	vlow	mod	mod	mod	hyperprolactinemia QTC prolongation
quetiapine	high	mod	low	mod	mod	QTC prolongation

Abbreviations: anticholinergic adverse effects (ACh AEs); extrapyramidal symptoms (EPS), very low (vlow), moderate (mod)

CATIE-AD trial reported a clinically-significant weight gain (0.12-0.14 lb/week of use) in female outpatients with AD treated with olanzapine and quetiapine while no weight gain was reported with risperidone and loss of weight was reported with placebo. Clinically-significant weight gain ($\geq 7\%$ of body weight) was associated with antipsychotic use for fewer than 12 weeks (OR=1.56; 95%CI=0.53-4.58), for 12 to 24 weeks (OR=2.89; 95%CI=0.97-8.64), and more than 24 weeks (OR=3.38; 95%CI=1.24-9.23) compared to patients who did not use antipsychotics during the trial. In addition, olanzapine was significantly associated with increased girth (0.07 inches/week) and decreased HDL cholesterol (-0.19 mg/dl/week). No changes were noted for blood pressure, blood glucose or triglycerides in males or females for all tested SGAs.⁵¹ It seems that while weight gain occurs with some SGAs in elderly populations with dementia, hyperglycemia and triglyceride elevations are less common. However, due to limited scientific data on this, recommended scheduled metabolic screening for and monitoring of the metabolic changes on commencement of a SGA and periodically thereafter is advisable.³⁶

In addition to above-mentioned SGA agent-specific adverse effects, all antipsychotics, as a class, are associated with serious safety concerns (i.e., increased risk for morbidity and mortality) in elderly populations with dementia. A large-scale meta-analysis of clinical trials found a 1.5-1.7 times increase in risk for death rate associated with antipsychotic use compared to placebo in elderly patients with dementia⁵²⁻⁵³ with the most frequently reported causes of mortality being aspiration pneumonia and cardiac-related complications such as sudden cardiac death. A meta-analysis of 15 placebo-controlled trials⁵² examined mortality risk among antipsychotics and placebo in dementia patients receiving olanzapine, risperidone, quetiapine or aripiprazole for 10-12 weeks. It found a small but statistically increased mortality risk (OR=1.54; 95%CI=1.06-2.23) compared to placebo. Risk was comparable among different SGAs.⁵²

A retrospective cohort study⁵⁴ using national data from the Department of Veterans Affairs (2001-2005) assessed 12-month mortality rates among outpatients >65 years of age treated with antipsychotic medication following a dementia diagnosis (n=10,615). All patient groups using antipsychotics had significantly higher mortality rates (22.6-29.1%) compared to patients who were not taking antipsychotic medications (14.6%). It is important to note that adjusted mortality risks for SGAs and for combined SGAs and typical antipsychotics were similar to those for typical antipsychotics. The increased mortality risk with

antipsychotics persists for at least 12 months. Rossom et al.⁵⁵ performed a retrospective cohort study including predominantly males aged 65 and older with dementia and treated with haloperidol (n=2,217), olanzapine (n=3,384), quetiapine (n=4,277), or risperidone (n=8,249). During the first 30 days, there was a significant increase in mortality in those with a daily dose of haloperidol > 1 mg (HR=3.2; 95%CI=2.2-4.5), olanzapine > 2.5 mg (HR=1.5; 95%CI=1.1-2.0), or risperidone > 1 mg (HR=1.6; 95%CI=1.1-2.2). On the other hand, quetiapine at doses below 50 mg/day and 50 mg or more/day were not associated with increases in mortality compared to the control group.⁵⁵

Another retrospective cohort study⁵⁶ used national data from the U.S. Department of Veterans Affairs on dementia outpatients ages 65 and older (n=33,604) who began treatment with risperidone, olanzapine, quetiapine, or haloperidol. The study reported differences in 180-day mortality rates among different treatment groups with antipsychotics. Haloperidol (RR=1.54, 95%CI=1.38-1.73) was associated with the highest mortality risk (risk was the highest in the first 30 days but decreased significantly and sharply thereafter). Among SGAs, risperidone (reference) was associated with the highest mortality risk, followed by olanzapine (RR=0.99; 95%CI=0.89-1.10) while quetiapine (RR=0.73; 95%CI=0.67-0.80) with the lowest mortality risk. The greatest differences in mortality risk were during the first 120 days of the treatment and declined in the subsequent 60 days.⁵⁷ Currently, the information about mortality associated with individual SGAs in patients with dementia is limited and further investigation is warranted, but it appears that increased risk persists 4-12 months.^{54,56} There is a need for large-scale comparisons of mortality associated with individual antipsychotic agents that would control for all important confounders, such as patient characteristics and antipsychotic dosage regimens.

It has been shown that elderly patients with dementia treated with atypical or conventional antipsychotics have a two-fold increase in risk for cerebrovascular adverse events (CVAEs) such as stroke and transient ischemic attack (TIA), especially during the initial weeks of treatment.^{27,53,57} A meta-analysis found that pooled rates of CVAEs (OR=2.1; 95%CI=1.2-3.8) were 1.9% in atypical antipsychotic treated patients compared to 0.9% in placebo-treated patients.²⁷ Kleijer et al.⁵⁷ performed a case-control analysis among community-dwelling patients (n=26,157; mean age=76) and found that participants with at least one current antipsychotic

prescription and recent exposure to antipsychotics were at an increased risk for CVAEs (OR=1.7; 95%CI=1.4-2.2) compared with non-users. The risk of CVAEs associated with antipsychotics in elderly patients is elevated during the first weeks of treatment. This risk decreases over time and is back to base level after 3 months of treatment. Chronic use was not associated with CVAEs.⁵⁷ The increased risk of CVAEs may be associated with pre-existing diabetes, hypertension or atrial fibrillation especially when poorly-controlled⁵⁸ as well as positive history of stroke or vascular dementia.⁵⁹ As a result of these findings, the use of all antipsychotics carries an FDA "black box" warning of increased morbidity and mortality among elderly patients with dementia.

CLINICAL PRACTICE IMPLICATIONS AND RECOMMENDATIONS

In the management of BPSD, it is important to initially rule out any underlying cause(s) or contributing factor(s) for a specific behavioral or psychiatric disturbance. These may include infection, delirium, hunger, pain, boredom and inattention, medication, and omission of use of glasses or hearing aids.^{15,30-33} When non-pharmacologic interventions alone are ineffective, the use of a selected SGA agent may be warranted for moderate to severe distressing physical aggression and for agitation and psychosis on a case-by-case basis after careful consideration of risks and benefits.^{15,30-33} Increased morbidity and mortality are very serious problems associated with the use of antipsychotics in elderly dementia patients and thus clinicians should always discuss the risks and benefits of antipsychotic use with the patient and/or his or her family and caregivers.^{15,30} In order to potentially decrease the risk of CVAEs, all modifiable cardiovascular risk factors such as diabetes, hypertension, atrial fibrillation and hyperlipidemia should be well-controlled to decrease risk for CVAE associated with the use of antipsychotics. In addition, SGAs should be used with caution in those individuals with hypovolemia and history of cerebrovascular and cardiac diseases.^{15,30} This raises a dilemma regarding use of an SGA in patients with VaD that are already at high risk for stroke or TIA.

A SGA should be initiated at a very low dose and should be slowly titrated up to the lowest effective dose to minimize adverse effects. Common target dose ranges in dementia for the management of agitation or distress with psychosis are usually in the lower range compared to other indications (aripiprazole 2-15 mg/day, olanzapine 2.5-10 mg/day, risperidone 0.25-3 mg/day, and quetiapine 25-100 mg/day), though these ranges are not universally

evidenced-based.³³ For patients with PDD and LBD, only quetiapine and clozapine should be used for management of aggression and psychosis due their sensitivity for antipsychotic-induced extrapyramidal symptoms. Low dose of quetiapine is usually preferred and is typically initiated at 12.5 mg in the evening with slow titration to maximal dose of 100 mg/day. Clozapine is not usually used as a first line therapy due to its risk for agranulocytosis and the need for frequent complete blood count monitoring.³⁹ Clozapine is usually started at 6.25 mg/day and slowly titrated, based on need, up to 75 mg/day. Treatment with antipsychotics should be carefully monitored for clinical efficacy, tolerability and safety and should not be continued indefinitely. The use of antipsychotics, including target BPSD symptoms, should be justified and well-documented in a patient's chart. One needs to keep in mind that use of all SGAs for management of BPSD is off-label and somewhat controversial because of their modest benefit versus risk profile in elderly patients with dementia. The BPSD symptoms typically wax and wane⁶⁰ and therefore the need for antipsychotic continuation should be regularly re-evaluated after 3-6 months of treatment.^{33,61} If unneeded, the SGA should be slowly tapered down and discontinued.

CONCLUSIONS

BPSD are very common, affecting nearly all dementia patients during the course of the disease. Management of individual BPSD remains a challenge. SGA benefits are uncertain, at best, with some reports of modest improvement of psychosis, agitation or aggression in dementia patients. These modest benefits need to be weighed against significant concerns regarding associated risk increases in mortality and morbidity. SGAs will continue to be prescribed due to the absence of more effective and safer alternatives. However, they should not be considered a "magic pill" to manage any BPSD in any dementia patient. The decision to treat with a SGA should be individualized on case-by-case need and their use and treatment targets should be well-documented. Appropriate use of SGAs for management of BPSD is critical to increase safety for our growing dementia population.

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How to cite this editor-reviewed article

Marvanova M. Antipsychotic use in elderly patients with dementia: Efficacy and safety concerns. *Ment Health Clin [Internet]*. 2014;4(4):170-6. Available from: <http://dx.doi.org/10.9740/mhc.n204371>