

Antipsychotics for Psychosis and Agitation in Persons with Dementia: Considerations for Use by Hospice and Palliative Care Providers

Joseph W. Shega, MD, Bansari Patel, APN ACHPN, Kavitha Ramchandran, MD

Cognitive loss and functional decline are characteristic of progressive neurodegeneration and are components of the clinical diagnosis of dementia. The majority of persons with dementia develop behavioral or psychological manifestations, although of the most common etiologies of dementia, Alzheimer's disease, vascular dementia, and Lewy body dementia, only the last includes these symptoms as part of the diagnosis. Psychosis (hallucinations, paranoia, and delusions) and agitation (aggression and irritability) are two symptoms that are particularly difficult to treat. They not only adversely affect the quality of life of patients and increase the likelihood of nursing home placement, but are also associated with higher rates of caregiver burden and depression. Moreover, no pharmacologic therapy has been approved by the FDA for the management of these symptoms in older adults with dementia. Given that behavioral and psychological symptoms occur most frequently in the later stages of the disease, hospice and palliative care practitioners require skills in their management.

A review of the assessment of psychosis and agitation is outside of the scope of this article; however, we include some considerations for clinicians as part of the evaluation process. The etiology of dementia in persons with psychosis is important to discern because the use of antipsychotics in persons with Lewy body dementia is frequently associated with a dramatic worsening of movement symptoms and can be fatal. Also, in contrast

to other forms of dementia, psychosis in Lewy body dementia frequently improves with cholinesterase inhibitor therapy.¹

Agitation is a complex symptom, and a variety of causes may affect its presence and severity. In addition to the underlying dementia, contributing causes may include physical or psychological symptoms, medical illness, medication effects, patient's fear or misunderstanding, environmental issues, or the dying process itself. Agitation should be distinguished from resistance to care as its evaluation and management are distinct. Treatment of the contributing causes of agitation may ameliorate the problematic behaviors so much that pharmacologic therapy with an antipsychotic would be unnecessary.

To help clinicians assess whether or not to prescribe an antipsychotic for these patients, we refer to the prescribing-rationale criteria proposed by Holmes for patients with advanced chronic illness.² This includes therapeutic efficacy (number needed to treat and number needed to harm), patient-specific considerations (remaining life expectancy and goals of care), and medication-specific considerations (time until benefit and appropriateness of treatment targets).

Therapeutic Efficacy

The empirical evidence supporting the use of antipsychotics for the management of psychosis and agitation in persons with dementia is fragmented and continues to be debated. The data presented below are derived from randomized controlled trials comparing atypical agents

(risperidone, olanzapine, quetiapine, and aripiprazole) to placebo presented in a metaanalysis conducted by LS Schneider and colleagues, a Cochrane Review, and the CATIE-AD trial.³⁻⁵ Overall, this research supports the claim that atypical antipsychotics are modestly effective but risky. Limitations of the currently available evidence include different outcome measures, making comparisons between studies difficult; varying quality of result reporting; a lack of attention to adverse events; and publication bias. Few studies of atypical antipsychotics incorporate clinically meaningful endpoints. Continuous scales measuring the severity of psychosis and agitation may display statistically significant differences between drug and placebo, but it is unclear whether these differences translate to demonstrable improvements in a patient's clinical status.

The meta-analyses by Schneider standardized the effect size from the different psychosis and agitation measures from published and unpublished studies to a one-standard deviation unit in an attempt to establish the efficacy of atypical antipsychotics.³ Overall antipsychotic use (risperidone, olanzapine, quetiapine, and aripiprazole) was associated with a standardized mean difference of a -0.16 ($P < .001$) decrease in behavioral scores compared to placebo. The separate standardized mean decreases in scores of each drug were: risperidone -0.18 ($P < .001$), olanzapine -0.11 ($P = .25$), quetiapine -0.17 ($P = .04$), and aripiprazole -0.22 ($P = .002$).

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Larger effect sizes were noted among participants without psychosis, those who reside in the nursing home, and those with more advanced dementia. It remains unclear whether the significant statistical differences found between treatment and placebo are clinically meaningful. As a comparison, Schneider points out the standard differences between active treatment and placebo found in the meta-analyses were similar in magnitude to the effects of cholinesterase inhibitors and memantine on cognition.

To help evaluate whether these findings are clinically meaningful, Schneider and colleagues used a surrogate measure of 30% to 50% improvement in psychosis and agitation scores from baseline.³ Using this endpoint from the studies where it was available, the number needed to treat to obtain clinical benefit from drug as compared to placebo ranged from 5 to 14. Between 25% and 30% of participants in the placebo arm had improvements in psychosis and agitation scores at the end of the study period, and atypical antipsychotics added an incremental benefit over this effect.

The Cochrane Review of published studies represents another assessment of the efficacy of atypical antipsychotics.⁴ In this meta-analysis, risperidone 1 mg and 2 mg daily were associated with a significant reduction in agitation scores compared to placebo with higher doses of risperidone associated with greater improvements. Risperidone usage was also associated with a significant reduction in psychosis symptoms. Use of 5 mg to 10 mg daily of olanzapine was also associated with a significant reduction in agitation scores, but no benefit was observed for psychosis symptoms. Data were not available to assess whether risperidone or olanzapine were associated with a clinically meaningful reduction in psychosis or agitation. Aripiprazole and quetiapine (somewhat newer atypicals) did not have enough published studies to permit combining results.

The Clinical Antipsychotics Trial of Intervention Effectiveness for Alzheimer's disease (CATIE-AD) was a double-blind controlled trial designed to assess the effectiveness of risperidone, olanzapine, and quetiapine compared to placebo in outpatients with Alzheimer's disease and

psychosis or agitation.⁵ Subjects were eligible for enrollment if psychosis or agitation were severe enough to disrupt daily function on a regular basis. The study attempted to mirror clinical practice in that doses were adjusted as clinically indicated by the study physician, and the treatment could be discontinued if it was not thought to be adequate after the first 2 weeks. The primary outcome was discontinuation of treatment to reflect patient, caregiver, and clinician opinion regarding efficacy and side effects. Other outcomes included minimal or greater improvement on the Clinical Global Impression of Change scale at 12 weeks, time to discontinuation due to lack of efficacy, and time to discontinuation due to adverse effects, intolerability, or death.

Although there was no difference overall among the four groups with regard to time of discontinuation of therapy ($P = .52$), the time of discontinuation due to lack of efficacy favored risperidone (26.7 weeks) and olanzapine (22 weeks) compared to quetiapine (9.1 weeks) and placebo (9 weeks).⁵ The time to discontinuation due to intolerance, adverse effects, or death favored placebo, with discontinuation rates of 18% for risperidone, 24% for olanzapine, and 16% for quetiapine, as compared with 5% for placebo. Overall, no difference existed between at least minimal improvement in impression of change between any antipsychotic and placebo ($P = .22$). However, olanzapine use was associated with greater improvement in global scores compared to placebo, with a number needed to treat of 9. The final dose of antipsychotics prescribed to participants was relatively low compared to other studies that demonstrated superior efficacy with atypical antipsychotics. The average daily doses prescribed in the CATIE-AD trial were risperidone 1.0 mg, olanzapine 5.5 mg, and quetiapine 55.6 mg, where the allowable range for each treatment was 0 mg to 2 mg, 0 mg to 17.5 mg, and 0 mg to 200 mg, respectively.

Adverse Effects

Atypical antipsychotics have a "black box" warning because their use has been associated with an increased risk of cerebrovascular events, including stroke and death. The absolute risk difference in such events between treatment and placebo was generally 1% to 2% with a relative risk

increase around 2 and a number needed to harm of 71.³ Atypical antipsychotic use was also associated with approximately a 1% to 2% increase in deaths compared to placebo, with a relative risk increase of 1.5 and a number needed to harm of 100.⁶ It appears that both an increased risk of a cerebrovascular event and death are a class effect—studies have not found that any one antipsychotic is associated with a greater risk.³ Taking into account the number needed to treat and harm, for approximately every 100 persons treated, 9 to 25 persons would be helped, and there would be one to two cerebrovascular events and one death. Atypical antipsychotic use is also associated with additional life-threatening side effects, including QT prolongation, the development of diabetes, and an increased risk of seizures.⁷

The more common side effects of these drugs include somnolence, extrapyramidal effects, edema, and infections. Given the poor quality of reporting adverse effects in most studies, a precise estimate of the incidence of side effects is difficult to determine. The CATIE-AD study found that the use of atypical antipsychotics was associated with a number of effects that can potentially diminish quality of life.⁵ Risperidone- and olanzapine-treated patients developed extrapyramidal signs 12% of the time compared with 1% of participants randomized to placebo (number needed to harm of 9). Sedation occurred in 15% of risperidone, 24% of olanzapine, and 22% of quetiapine participants, but only in 5% of placebo patients (number needed to harm between 5 and 10). Confusion was also more common among antipsychotic users with 11% of risperidone and 18% of olanzapine users developing cognitive changes compared to 5% of placebo (number needed to harm between 8 and 17). Participants taking atypical antipsychotics were also more likely to gain weight and have increases in body mass index compared to placebo. Additional side effects noted in the meta-analysis by Schneider or the Cochrane Review include edema, urinary tract infections, and upper respiratory tract infections.^{3,4} Finally, it is important to recognize that typical antipsychotics (haloperidol and chlorpromazine) are associated with a higher likelihood of sedation and extrapyramidal side effects compared to the newer atypical agents.⁸

Patient-Specific Considerations

Even though a precise estimate of remaining life expectancy is difficult to assess in persons with dementia, the development of psychosis and agitation typically occurs in the moderate to more advanced stages of the disease. Given this, the risks of antipsychotic therapy may be more acceptable for persons with more severe dementia. In fact, near the end of life adverse events such as sedation may be a desired secondary effect and even provide an argument for the use of a typical rather than atypical antipsychotic.

Given the difficulty in estimating prognosis, it is important to delineate the goals of medical care when deciding whether to prescribe an antipsychotic for psychosis and agitation. Families may be more comfortable accepting the risks of antipsychotic therapy when the goals are predominately palliative. However, the risks of therapy may outweigh the benefits for someone with moderate dementia who has psychosis or agitation, but is otherwise highly functioning. As dementia progresses and remaining life expectancy decreases, the goals of care may shift toward comfort, so the benefits of antipsychotic use may outweigh the risks.

Medication-Specific Considerations

As with other therapies with a narrow therapeutic window, the initiation and titration of antipsychotics should follow the principle of starting low and going slow. Clinical trials suggest a response to antipsychotic therapy is likely by 2 to 4 weeks after initiation.^{3,4} At that time, providers can decide whether to continue the current dose, increase the dose, change to a different antipsychotic, or stop the therapy altogether. Once the therapeutic dose of the antipsychotic is achieved, a standing dose is usually prescribed to prevent psychosis and agitation. If the patient is actively dying, the antipsychotic dose can be escalated more rapidly, usually with a doubling of the dose after the drugs reach their peak effect. It is important to make families aware that this approach will attenuate symptoms more rapidly, but will also result in more side effects.

Defining and monitoring treatment targets is key to ensuring optimal prescribing of antipsychotics for psychosis and agitation in persons with dementia.

Experts recommend that antipsychotics not be used unless symptoms are severe enough to interfere with daily functioning or be extremely distressful to the patient. If the target behavior is well controlled by the drug, one should consider continuing the therapy for 8 to 12 weeks. At that time, it is probably prudent to taper or discontinue the antipsychotic because the frequency and severity of psychosis and agitation vary substantially over time.

Atypical antipsychotics are modestly effective for the treatment of psychosis and agitation in persons with dementia. Efficacy is tempered by substantial side effects including sedation, extrapyramidal signs, cerebrovascular events, and death. The incorporation of antipsychotics into the care plan requires a thoughtful consideration of symptom severity and the relative risks and benefits of therapy. The latter argument includes consideration of remaining life expectancy, the goals of care, appropriate dosing, and defining and monitoring treatment targets. ◡

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Joseph W. Shega, MD, and Bansari Patel, APN ACHPN, are professors in the department of geriatrics and palliative medicine at the University of Chicago. Kavitha Ramchandran, MD, is a professor in the division of hematology and oncology at Northwestern University. Please address comments to Dr. Joseph Shega at jshega@gmail.com.