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The Role of Antipsychotic Drugs in the Treatment of Neuropsychiatric Symptoms of Dementia

Abstract: Patients with dementia frequently experience comorbid behavioral and psychiatric symptoms, also known as neuropsychiatric symptoms of dementia. Neuropsychiatric symptoms are harmful to both patients and their caregivers, and contribute to the high healthcare costs associated with Alzheimer's dementia. Since the discovery of neuroleptic medications in the 1950s, antipsychotic medications have been the preferred drug option for the treatment of behavioral and psychiatric symptoms of dementia. Despite their frequent use in the past, there is limited evidence to support the efficacy of first-generation antipsychotics in this population. Second-generation antipsychotics may be modestly helpful for reducing global neuropsychiatric symptoms, psychosis, and agitation/aggression in demented older adults. However, second-generation antipsychotics are associated with potentially serious adverse reactions in elderly adults, which may undermine the potential benefits. In clinical practice, second-generation antipsychotics are prescribed for demented patients with distressing or dangerous behavioral disturbances that fail to respond adequately to nonpharmacological approaches. The decision to utilize an antipsychotic requires thoughtful consideration of the potential risks and benefits for the individual patient.

In the United States, an estimated 5.4 million elderly adults have Alzheimer's Dementia (AD), and that number is expected to triple by 2050 (1). At any given point in time, 61% of patients with AD are experiencing at least one neuropsychiatric symptom (2), also known as behavioral and psychological symptoms of dementia. Moreover, approximately 60%–90% of community-dwelling patients with dementia experience neuropsychiatric symptoms as part of their illness, which suggests that all patients with dementia are at high risk of developing neuropsychiatric symptoms (2, 3). Neuropsychiatric symptoms include apathy, mood disturbances, hallucinations, delusions, aggression and agitation. Since 1996, when the International Psychogeriatric Association combined all "signs and symptoms of disturbed perception, thought content, mood or behavior that frequently occur in dementia" under the umbrella of "behavioral and psychological symptoms of dementia," efforts have been made to define each of these symptoms individually (4, 5). Of these symptoms, "agitation" is the most difficult to define and is often used interchangeably with other ill-defined terms such as "behavioral disturbance" and "disruptive behavior." Cohen-Mansfield (6) defines agitation as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to be an obvious outcome of

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the needs or confusion of the individual." Aggressive behaviors, a subset of agitated behaviors, are defined as "overt acts involving delivery of noxious stimuli toward others" (7). The frequency of individual symptoms varies widely by dementia type, disease severity, setting, and study methodology. Reported prevalence rates in patients with AD are as follows: hallucinations (4%–44%), delusions (9%–63%), aggression (11%–46%), and agitation (20%–80%) (8). To date, there is no FDA-approved treatment for neuropsychiatric symptoms of dementia. In the absence of safe and effective treatment alternatives, antipsychotic agents are frequently used off-label as a first-line treatment option (9).This article summarizes what is known about the benefits and risks of antipsychotic agents and alternative therapies for the treatment of psychotic symptoms, aggression, agitation, and global neuropsychiatric symptoms in patients with AD.

Clinical context

Left untreated, neuropsychiatric symptoms are associated with significant risks to both patients and their caregivers. Patients may experience lower quality of life, poorer prognosis, and increased mortality (8). Neuropsychiatric symptoms are also associated with increased caregiver burden and stress (10), earlier nursing home placement (11), and greater healthcare costs (12). If nonpharmacological interventions have failed, an atypical antipsychotic is often prescribed as a first-line drug option (8, 13). Medications commonly used as second-line options include antidepressants, mood stabilizers, and cognitive enhancers (14), although evidence supporting efficacy of these medications is currently very limited.

In 2005, the FDA issued a black box warning of an increased risk of mortality associated with the use of second-generation, or atypical, antipsychotic medications in elderly patients with dementia (15). A similar warning was issued for first-generation, or typical, antipsychotics in 2008 (16). Despite the black box warnings, antipsychotics are frequently prescribed to demented elderly patients with neuropsychiatric symptoms (9, 17). This article provides an overview of the evidence regarding the efficacy and safety of atypical antipsychotics in the treatment of psychosis, aggression, and agitation of AD. Next, the known risks and benefits of alternative options, including pharmacological and nonpharmacological treatments, are discussed. Finally, recommendations for the appropriate use of atypical antipsychotics within the context of a broader treatment approach are provided.

Treatment strategies and evidence

First-generation antipsychotics

The first neuroleptic agent, chlorpromazine, was first prescribed in the 1950s. Until the introduction of the second-generation antipsychotics (SGAs) in the early 1990s, first-generation antipsychotics (FGAs) were prescribed off-label for agitation and aggression in demented older adults with very little supporting efficacy and safety data in this population. There is no evidence that haloperidol, or other FGAs, reduce global neuropsychiatric symptoms of dementia (11). However, haloperidol may be effective for the treatment of aggression, but not agitation (18). Like the atypical antipsychotics, FGAs are associated with adverse reactions, including sedation, QTc prolongation, abnormal gait, falls, and syncope (18, 19). In elderly patients, FGAs carry a higher risk of extrapyramidal symptoms (EPS), including irreversible tardive dyskinesia, compared with second-generation antipsychotics (14). According to a recent retrospective cohort study, haloperidol has 1.5 times the risk of mortality of SGAs, especially within the first 4 weeks of treatment (20). In a review of the comparative effectiveness of antipsychotics for off-label uses, FGAs were found to have a mortality risk equal to or greater than that of the SGAs (21). Considering the overall lack of evidence supporting the efficacy of FGAs, combined with the increased risk of serious adverse events compared with newer antipsychotics, FGAs are not usually recommended for the treatment of neuropsychiatric symptoms in demented older adults.

Second-generation antipsychotics

Since clozapine was introduced in 1989, 10 second-generation antipsychotics have been FDA-approved for use in the United States. Also known as atypical antipsychotics, risperidone, olanzapine, quetiapine, and aripiprazole are the most frequently prescribed SGAs in elderly patients. In contrast to the lack of data regarding the safety and efficacy of most classes of psychotropic agents used in older adults, several well-designed clinical trials have examined the efficacy of SGAs in elderly patients with AD. To date, 18 randomized-controlled trials (RCTs) investigating the use of SGAs in elderly demented adults over 6 to 12 weeks have been completed. A meta-analysis comprising 15 of the RCTs concluded that the atypical antipsychotics aripiprazole and risperidone demonstrated efficacy for neuropsychiatric symptom reduction according to rating scales

(22). Patients who showed the most benefit from an SGA had severe cognitive impairment, lacked psychotic symptoms, and lived in a nursing home (22). The effect sizes were small, with a calculated number needed to treat (NNT) ranging from 5 to 14. Both active treatment and placebo groups improved somewhat from baseline, usually within the first 4 weeks. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study evaluated the effectiveness of atypical antipsychotics in outpatients with AD and psychosis, agitation, or aggression (23). In phase I of the trial, subjects were randomly assigned to risperidone, olanzapine, quetiapine, or placebo (24). The protocol allowed the prescribing clinician to change the blinded treatment at any time, based on symptom response or adverse effects. There was no difference between placebo and SGAs for the primary outcome of time to any-cause discontinuation of the initially assigned drug. Risperidone and olanzapine were more effective than placebo, based on time to discontinuation due to lack of efficacy. Quetiapine showed no benefit over placebo, possibly due to inadequate dosing. Subjects in the placebo group were less likely than those on any active drug to discontinue the intervention due to adverse reactions or drug intolerance. Average doses at the end of phase I were as follows: olanzapine, 5.5 mg/day; quetiapine, 56.5 mg/day; and risperidone, 1.0 mg/day (24). The authors concluded that SGAs produce small, but likely clinically significant, reductions in behavioral symptoms of dementia. In a follow-up analysis of individual target symptoms in the CATIE-AD trial, hostile, aggressive, and paranoid behaviors responded more prominently to antipsychotic drug treatment than did anxious, excitable behaviors; psychosis improved most with risperidone treatment (24). In other analyses, antipsychotic treatment reduced caregiver burden (10) but did not improve daily functioning, quality of life, or caregiver time needed (24). In September 2011, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on off-label uses of SGAs (21). Eighteen RCTs of atypical antipsychotics in dementia, ranging from 6 to 12 weeks duration, were included in the pooled analysis. Dosages used in the studies ranged from 0.5 to 2.5 mg/day for risperidone, 1 to 15 mg/day for olanzapine, 25 to 600 mg/day for quetiapine, and 2 to 15 mg/day for aripiprazole. Treatment with aripiprazole, olanzapine, or risperidone resulted in small but statistically significant improvements in both global neuropsychiatric symptoms and agitation specifically, versus placebo. Only risperidone improved psychotic symptoms. In terms of comparative effectiveness, no difference was found between risperidone and olanzapine or aripiprazole. Taken together, there is strong evidence that risperidone, olanzapine, and aripiprazole lead to modest reductions in global neuropsychiatric symptoms and agitation or aggressive behaviors specifically in AD. Risperidone may have particular benefit for the treatment of psychotic symptoms associated with dementia. Important variables such as the minimum effective dose, optimal duration of treatment, and specific patient characteristics that influence the extent of response to a particular medication remain unclear. The key question facing clinicians is whether the modest symptomatic improvements conferred by SGAs offset the potential adverse events.

QUESTIONS AND CONTROVERSY

Atypical antipsychotics are associated with serious adverse events in elderly adults, especially those with dementia. In 2005, the FDA issued a public health advisory reporting a 1.6 to 1.7-fold increase in mortality for older adults with dementia treated with an SGA (15). Most deaths were attributed to heart failure, sudden death, or pneumonia. Since then, published reports have substantiated the increased mortality risk associated with SGAs. A meta-analysis of 15 RCTs, lasting from 10 to 12 weeks in duration, evaluated the risk of death in patients with AD treated with risperidone, olanzapine, quetiapine, or aripiprazole (25). Analysis of pooled data revealed an increased risk of death in the active drug group versus placebo (odds ratio [OR] 1.54, 95% confidence interval [CI]=1.06–2.23; p=0.02). Meta-analysis of each individual drug did not reveal any statistically significant increased mortality risk. The authors calculated a number needed to harm (NNH) of 100, and estimated that for every 9 to 25 patients who improved on the medication, there would be one additional patient death. A recent retrospective cohort study evaluated the mortality risk of individual antipsychotics over 6 months of follow-up (20). Of the SGAs, risperidone and olanzapine showed an intermediate mortality risk, while quetiapine had the lowest risk. The death risk associated with SGAs was highest within the first 4 months of treatment and declined over the remaining 2 months of follow-up. In summary, there appears to be a small increased risk of death associated with SGAs. How atypical antipsychotics may be contributing to patient deaths is unknown. Furthermore, it is unclear whether the increased risk of death is specific to antipsychotics or may also be associated with other classes of psychotropic medications.

In addition to the increased risk of death, SGAs are associated with a small increase in risk of

cerebrovascular events. Data from RCTs and observational studies suggest that atypical antipsychotics are associated with a two- to threefold increased risk of minor strokes (26). Patients with a history of vascular risk factors or vascular dementia are likely to be at higher risk of cerebrovascular adverse events (27). Strokes may be more common in subjects treated with risperidone (NNH=34) and olanzapine than with other SGAs (28).

Furthermore, SGAs are associated with other more common and potentially serious side effects. Atypical antipsychotics may lead to prolonged QTc, predisposing patients to cardiac arrhythmias. Cardiovascular events are especially common with risperidone (NNH=53) and olanzapine (NNH=48) (28). Olanzapine should be avoided in patients with a history of syncope due to an increased risk of orthostatic hypotension (19). Olanzapine also decreases the seizure threshold and should be avoided in patients with seizures (19). All SGAs except clozapine and quetiapine are associated with an increased risk of extrapyramidal symptoms in the elderly. Extrapyramidal symptoms are most common with risperidone (NNH=20), olanzapine (NNH=10), and aripiprazole. All SGAs are associated with an increased risk of falls and hip fractures, although it is unclear if this risk is specific to antipsychotic agents (19, 26, 27). Metabolic effects of SGAs in the elderly population have not been well studied. In the CATIE-AD trial, women treated with olanzapine showed significant weight gain and decreased HDL levels but no significant changes in blood pressure, glucose, or triglyceride levels (29). In a pooled analysis, both olanzapine (NNH=24) and risperidone (NNH=25) were associated with weight gain (21). Sedation (NNH=8–16) and fatigue (NNH=18 – 21) commonly occur with all SGAs (21). In the CATIE-AD trial, subjects treated with risperidone, olanzapine, and quetiapine demonstrated a clinically significant acceleration of cognitive decline over 36 weeks that was, on average, equivalent to 1 year's deterioration due to the natural progression of AD (30). However, a randomized placebo-controlled trial designed to assess cognitive decline associated with continued antipsychotic use over 6 months versus discontinuation failed to find an association between antipsychotic treatment and cognitive decline (31).

In 2012, the American Geriatric Society (AGS) published updated Beers Criteria listing medications that are potentially inappropriate for use in older adults (19). Based on the increased risk of death and stroke, clinicians are advised to avoid the use of all antipsychotics in older adults. In cognitively impaired elderly patients, antipsychotics should be avoided unless nonpharmacological options have failed, and the patient continues to be an imminent threat to themselves or others as a result of psychosis, agitation, or aggressive behaviors (19). In usual clinical practice, antipsychotic medications are reserved for those dementia patients with psychosis or agitated/aggressive behavior that is markedly distressing for the patient or that promotes concern for patient or caregiver safety.

Given the serious risks associated with SGAs, clinicians seeking safe and effective alternatives have turned to other psychotropic medications, including antidepressants, cognitive enhancers, mood stabilizers, and benzodiazepines. Unfortunately, there are few trials investigating the efficacy and safety of these agents in elderly adults with dementia and behavioral disturbances, and the available efficacy studies produced mixed results (8, 11, 13). Valproate preparations are frequently prescribed as alternatives to SGAs in spite of the lack of evidence of efficacy for the treatment of agitation (32). Valproate preparations are associated with adverse events in elderly patients, including falls, infections, and death (19, 20, 32). Among the antidepressants, citalopram in particular appears promising. In a 12-week RCT comparing risperidone and citalopram for the treatment of hospitalized patients with dementia, citalopram was associated with a reduction of psychotic symptoms and agitation (33). To further evaluate the safety and efficacy of citalopram in patients with dementia, the citalopram for agitation in AD (CitAD) trial is nearing completion (34). However, the usefulness of citalopram in the treatment of elderly adults may be limited by safety concerns and revised dosing guidelines. In 2011, the FDA issued a drug safety announcement informing physicians of dose-dependent QTc interval prolongation associated with citalopram (35). Due to the potential risk of serious abnormal heart rhythms with higher doses of citalopram, the FDA recommends a maximum daily dose of citalopram of 20 mg/day in adults over the age of 60. Researchers are exploring additional novel therapeutic agents for the treatment of psychosis, agitation, and aggression in AD, in addition to investigating medications that are FDA-approved for other indications. At this time, there is insufficient evidence to conclude that other psychotropic medications are as safe or effective as SGAs.

Because of the modest beneficial effects, on average, and the potential adverse events of current medications, clinicians are advised to try nonpharmacological measures prior to resorting to medications. A growing body of evidence supports the use of nonpharmacological interventions. Livingston et al. reported that behavioral management techniques, caregiver psychoeducation, music therapy,

and staff education reduced behavioral symptoms (36). However, only nine of the studies were considered to be high quality. A review of three RCTs and six single-case design trials supported the benefits of individualized behavioral interventions (37). In 2009, a systematic review of RCTs and repeated measures studies reported small to moderate, but short-lived, improvements in behavioral symptoms with aromatherapy, bed baths, individualized music, and muscle relaxation techniques over an attention control (38). These interventions were especially effective when individualized to the patient. In a recent meta-analysis investigating home-based psychosocial interventions for community-dwelling patients with dementia, 23 high-quality studies of nonpharmacological interventions were found, including 16 RCTs (39). In some of the studies, caregiver interventions consisting of 9 to 12 sessions tailored to the needs of the patient and their caregiver, reduced neuropsychiatric symptoms. Effect sizes were occasionally larger than those achieved with antipsychotic treatment and no adverse events were reported. Thus, recent evidence suggests that nonpharmacological interventions, when individualized to the specific needs of the patient and caregiver, may be helpful in reducing neuropsychiatric symptoms of dementia. However, further studies are needed to confirm the efficacy of nondrug therapies. There is little data available to guide physicians in the use of nonpharmacological approaches. Most nonpharmacological interventions consist of multiple components that are potentially therapeutic, and the particular element resulting in benefit remains unknown. Further research is needed to determine the specific interventions that are most appropriate for particular target symptoms. Barriers to implementing nondrug measures include insufficient caregiver knowledge, limited resources, pressure from nursing staff to prescribe medication, and lack of reimbursement mechanisms (6, 40). Faced with these obstacles, it is no wonder that while most physicians prefer to utilize nonpharmacological interventions as first-line treatment options, medications continue to be used as often as nonpharmacological therapies for the treatment of neuropsychiatric symptoms of dementia (40).

RECOMMENDATIONS FROM THE AUTHORS

Based on the available evidence, the following approach to treatment is recommended:

1. *Counsel patients and their caregivers before neuropsychiatric symptoms occur (13).* Educate patients and their caregivers about the risk of developing neuropsychiatric symptoms. Discuss goals of care, taking into account the patient's individual preferences, values, and culture. Advise the patient and caregiver of the risks and benefits of treatments for behavioral disturbances, including the option of nonpharmacological therapies, and document the discussion of shared decision-making. Measure and document the patient's baseline cognitive, psychiatric, and behavioral symptoms and functional status.
2. *Identify and document specific target symptoms and symptom severity (8).* Consider using a rating scale such as the Neuropsychiatric Inventory (NPI), Clinical Global Impression of Change (CGIC), or Brief Psychiatric Rating Scale (BPRS) to document baseline symptoms.
3. *When neuropsychiatric symptoms occur, begin a thorough medical, neurological, and environmental assessment (8, 27).* Treatment begins with a comprehensive search for underlying causes. Perform a medical assessment, including a thorough physical exam and basic laboratory tests. Specifically assess for uncontrolled pain, infections, and dehydration, which are common underlying precipitants of behavioral disturbances. A genitourinary exam should not be overlooked, particularly in female patients. As part of the neurological exam, evaluate the patient's level of alertness and cognitive status. Behavioral disturbances may be due to a delirium superimposed on the underlying dementia. Review the medication list for recent changes, drug-drug interactions, and polypharmacy. Valuable history from the patient's caregivers may reveal environmental factors contributing to behavioral changes.
4. *Select an appropriate intervention based on the initial assessment.* In patients with mild symptoms, a period of watchful waiting may be appropriate to allow time for further evaluation of the underlying cause. For patients with more significant symptoms, begin a 1-week trial of tailored nonpharmacological interventions (13). If the patient fails to respond to nonpharmacological measures and the target symptoms are distressing or dangerous to the patient or others, it is reasonable to consider a trial of an SGA (8, 19, 21). In addition to symptom severity, multiple factors specific to the patient alter the risk-benefit balance, including the value of modest behavioral improvement for the individual, current health status, vulnerability to adverse effects, response

to other interventions, and patient and caregiver preference. Prior to starting an antipsychotic, discuss the risks and benefits of SGAs versus the risks and benefits of alternative therapies with the patient and their family or caregiver. Obtain written informed consent and document the discussion in the medical record. As in younger adults, evaluate baseline metabolic laboratory and ECG results prior to starting any antipsychotic. Typical starting and maintenance doses of commonly prescribed SGAs are provided in Table 1.

5. *Evaluate for target symptom response and adverse events within 1 to 4 weeks of initiating an SGA (8, 28).* Consider remeasuring target symptoms using a rating scale to document improvement. If the patient shows an inadequate response to an SGA, consider raising the dose within the usual limits shown in Table 1, if there have been no adverse effects. Other preferred strategies include a retrial of nonpharmacological interventions, switching to another SGA (22), or trial of a drug outside the antipsychotic class, acknowledging that evidence of benefit and safety in clinical trials are lacking for nonantipsychotic drugs.
6. *Monitor patients on SGAs closely, especially during the first 3 to 6 months of treatment (20).* Assess response to treatment, including medication tolerance and adverse effects. Recall that patients are at highest risk of death within the first 6 months after starting an SGA. Repeat laboratory testing for metabolic effects at months 3 and 6, and then every 6 months while on an SGA (8).
7. *Consider a trial of discontinuation (8, 27, 41).* Discontinue the antipsychotic if the patient fails to respond within 1 to 3 months (22). Patients suffering from severe target symptoms at baseline who respond well to an SGA may benefit from continued SGA treatment (31, 42). The decision to withdraw or continue an antipsychotic depends on the risk and consequences of recurrent symptoms, the severity of side effects, patient vulnerability to potential adverse events, and preference of the patient and caregiver. If ongoing treatment with an antipsychotic is warranted, clearly document the risks of discontinuation and benefits of continued drug treatment.

Table 1. Typical Starting and Maintenance Doses of Commonly Prescribed Atypical Antipsychotic Medications

Drug	Starting Dose (mg/day)	Maintenance Dose (mg/day)
Aripiprazole	2–5	5–15
Olanzapine	2.5–5	2.5–10
Quetiapine	12.5–25	25–200
Risperidone	0.25–0.50	0.25–1.50

Summary

Behavioral and psychiatric symptoms are common in patients with AD, and are associated with adverse outcomes for both patients and caregivers. Management of psychosis, agitation, and aggression of dementia begins with a careful assessment for contributing factors, identifying the specific symptoms that are present, and targeted nonpharmacological interventions; however, further research is needed to evaluate the efficacy of nondrug therapies. If the patient fails to respond to nondrug interventions, pharmacological options should be considered. At this time, SGAs are the only class of psychotropic agents with reasonably consistent evidence of efficacy in older adults with dementia. Patients with severe or distressing global neuropsychiatric symptoms, psychosis, agitation, or aggression may benefit from treatment with an SGA. The decision to utilize an SGA requires careful consideration of the risks and benefits for the individual patient and should be made in collaboration with the patient and their caregiver.

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