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Dr. Kales: Risks and benefits of antipsychotics and other psychotropics for behavioral and psychological symptoms of dementia

THIRD OF 3 PARTS

Prescribing antipsychotics in geriatric patients: Focus on dementia

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When to use SGAs for behavioral and psychological symptoms of dementia

According to the U.S. Department of Health and Human Services, in 2007, 88% of 1.4 million Medicare claims for second-generation antipsychotics (SGAs) in older adult nursing home residents were associated with a dementia diagnosis. Similar trends have been observed in Canada and Europe.[1-4] In a retrospective analysis of medication data from older residents with dementia in 6 care homes in England, long-term (ie, >1 month) use of antipsychotics was the most frequent potentially inappropriate prescribing practice.[3] In another study in 7 European countries and Israel, the overall prevalence of antipsychotic use among long-term care residents with dementia was 33%.[1] Similarly, a recent literature review[5] found that 22% to 86% of antipsychotic prescriptions to older individuals were off-label; this practice was particularly common for individuals with agitation.

Because of the aging population and widespread prescription of antipsychotics to older patients, clinicians need information on the relative risks of using these medications in this population. In the United States, all antipsychotics carry a FDA "black-box" warning of the increased risk of death in

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older adults with dementia. In addition, the risk of death is increased when prescribing antipsychotics to older adults with other conditions, such as Parkinson's disease,[6] and other safety and tolerability concerns, including falls and fractures, sedation, metabolic abnormalities, and extrapyramidal effects, are highly relevant to geriatric patients.

This 3-part review summarizes findings and recommendations on prescribing antipsychotics to older individuals with schizophrenia, bipolar disorder, depression, and dementia. This third and final installment:

- briefly summarizes the major studies and analyses relevant to prescribing antipsychotics to older patients with dementia
- provides a summative opinion on safety and tolerability issues in these older patients
- highlights the gaps in the evidence base and areas that need additional research.

Summary of benefits, place in treatment armamentarium

Behavioral and psychological symptoms of dementia (BPSD) include agitation, delusional beliefs, repetitive questioning, hallucinations, aggression, wandering, and various socially inappropriate behaviors.[7] These occur almost universally in all types and stages of dementia.[7] BPSD are among the most complex, stressful, and costly aspects of dementia care, and lead to a myriad of poor health outcomes, including excess morbidity, mortality, hospital stays, and early nursing home placement.[8-11] Because BPSD usually occur across all types and stages of dementia,[7,12-16] the prevalence of BPSD mirrors the overall prevalence of dementia.

Although all expert organizations, including the American Psychiatric Association,[17] recommend nonpharmacologic strategies as first-line treatment for BPSD, for the most part, these recommendations have not been translated into standard clinical management or routine care.[18] Because of a perceived lack of other options, the current mainstay of treatment is the off-label use of psychotropics such as antipsychotics. Of all the agents currently used for BPSD, SGAs have the strongest evidence base, although benefits are modest at best (standardized effect size 0.13 to 0.16).[19,20] In terms of individual SGAs, only risperidone is indicated for aggression in Canada and in Europe (not in the United States); risperidone has the best evidence for efficacy, with a meta-analysis of 5 published randomized controlled trials (RCTs) reporting that risperidone is superior to other SGAs for aggression in dementia.[21,22] As a class, first-generation antipsychotics (FGAs) have no clear evidence for BPSD as defined broadly; however, there may be slight benefit for haloperidol for aggression.[23,24]

Clinical Trials

Adverse effects. A meta-analysis of RCTs of SGAs found that, compared with placebo, SGAs have increased rates of several adverse effects. These include somnolence (17% drug vs 7% placebo; odds ratio [OR], 2.84; 95% confidence interval [CI], 2.25 to 3.58; $P < .00001$); extrapyramidal symptoms (13% drug vs 8% placebo; OR, 1.51; 95% CI, 1.20 to 1.91; $P = .0005$; primarily attributable to risperidone); abnormal gait (10% drug vs 2% placebo; OR, 3.42; 95% CI, 1.78 to 6.56; $P = .0002$; attributable to olanzapine and risperidone); edema (9% drug vs 4% placebo; OR, 1.99; 95% CI, 1.20 to 3.30; $P = .008$; attributable to olanzapine and risperidone); urinary tract infections/incontinence (16% drug vs 12% placebo; OR, 1.28; 95% CI, 1.02 to 1.61; $P = .04$); cognitive impairment measured as difference in Mini-Mental State Examination score (95% CI, 0.38 to 1.09; $P < .0001$)[25]; and stroke (1.9% drug vs 0.9% placebo, OR, 2.13; 95% CI, 1.20 to 3.75; $P = .009$).[21,26]

In the 42-site Clinical Antipsychotic Trials of Intervention Effectiveness Alzheimer's disease RCT, 421 outpatients with Alzheimer's disease and BPSD were randomized to an SGA (risperidone, olanzapine, or quetiapine) or placebo. Compared with placebo, SGAs had a higher rate of parkinsonism or extrapyramidal signs (olanzapine and risperidone groups); sedation; confusion/changes in mental status (olanzapine and risperidone); psychotic symptoms (olanzapine); and increase in body weight and body mass index.[26]

continued

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Clinical Point

SGAs have the strongest evidence base for BPSD, although benefits are moderate at best

Clinical Point

Although there is limited data on cardiac adverse effects, 1 study found an increase in those taking FGAs compared with SGAs

In the 2005 FDA black-box warning, pneumonia and cardiac adverse effects were cited as primary causes of death for patients with dementia taking SGAs. A subsequent observational study confirmed that use of either FGAs or SGAs in geriatric patients was associated with an increased risk of pneumonia, in a dose-dependent manner.[27] Although there is limited data on cardiac adverse effects in older adults, especially those with dementia taking antipsychotics,[28] 1 observational study of nursing home residents[29] found that those taking FGAs had a significantly higher risk of hospitalization for ventricular arrhythmia or cardiac arrest compared with those who were not taking FGAs. In contrast, there was no increased risk with SGAs.

Mortality. In 2005, the FDA announced that based on a reanalysis of 17 placebo-controlled trials (many of which were unpublished) that SGAs were associated with a 1.7-fold increase in mortality compared with placebo.[30] As a result, the FDA issued a black-box warning for using SGAs in patients with dementia. The overall OR in a published meta-analysis of mortality with SGAs was 1.54 (1.06 to 2.23; z = 2.28; *P* = .02), with pooled events of 3.5% mortality vs 2.3% (drug vs placebo).[21] This meta-analysis[21] also included ad hoc analyses of haloperidol; using combined data from 2 contrasts of haloperidol (with risperidone and quetiapine; 243 patients receiving haloperidol and 239 receiving placebo) they also found 15 deaths (6.2%) with haloperidol and 9 (3.8%) with placebo, resulting in an OR of 1.68.

Other clinical data

Observational studies. Most observational studies have confirmed concerns regarding increased mortality in patients with BPSD who take antipsychotics, with FGAs having a higher risk than SGAs[18,31] and SGAs having a higher risk compared with most other psychotropics.[32] Three studies that found no increase in mortality with antipsychotics in patients with dementia had methodological issues, including examining prevalence as opposed to new users,[33,34] not controlling for exposure,[10,33,34] power issues,[10,34] not controlling for other psychiatric medications,[10] and varying lengths of follow-up.[10] An FDA black-box warning for FGAs was announced in 2008[30] based on 2 observational studies that showed an increased risk of mortality in older adults taking FGAs vs SGAs.[35,36]

In terms of specific SGAs, Kales et al[37] examined the mortality risk associated with individual antipsychotics using various methods to control for confounding. Among a national sample of >33,000 older veterans with dementia newly started on haloperidol, risperidone, olanzapine, quetiapine, or valproic acid and derivatives (as a nonantipsychotic comparator), the highest mortality across all analyses (intent to treat, exposure, propensity-adjusted) was associated with haloperidol, followed by risperidone and olanzapine, valproic acid, and quetiapine.

Most recently, a retrospective case-control study (90,786 patients age ≥65 with dementia) examined the number needed to harm (NNH; ie, number of patients needed to receive treatment that would result in 1 death) over 180 days following initiation of an FGA or SGA.[38] This study found the following NNHs: haloperidol, 26 (95% CI, 15 to 99); risperidone, 27 (95% CI, 19 to 46); olanzapine, 40 (95% CI, 21 to 312); and quetiapine, 50 (95% CI, 30 to 150).[38] These results are congruent with a review of observational studies that found the highest risk of mortality was associated with haloperidol and chlorpromazine, and the lowest risk with olanzapine, quetiapine, and ziprasidone.[28]

Patterns of antipsychotic use in older dementia patients

There are high rates of antipsychotic use in patients with dementia. Before the FDA issued the black-box warning, the Aging Demographics and Memory study found that the rate of antipsychotic use in community (outpatient) older adults with dementia was approximately 19% between 2002 and 2004 in a representative sample of 307 older adults.[39] Another study examining trends in community antipsychotic use in the U.S. Department of Veterans Affairs (VA) found that in the 1990s, SGA use was increasing;

approximately 18% of outpatients with dementia were taking these agents.[40] Use of SGAs began to decline in 2003, ahead of the 2005 black-box warning, in tandem with other advisories (eg, diabetes, metabolic syndrome,[41] and stroke risk).[42,43] Olanzapine and risperidone showed declining rates between 2003 and 2005, whereas quetiapine use significantly increased during this period. All 3 SGAs declined after the black-box warning. However, by the end of 2007, the use of SGAs had leveled off to approximately 12% of VA patients with dementia. A recent U.S. Government Accountability Office (GAO) report found that in 2012, 14% of older adult Medicare Part D enrollees with dementia living in the community were prescribed an antipsychotic.[44]

Use in nursing home residents. Because BPSD are one of the main reasons people with dementia are placed in nursing homes, it is not surprising that rates of antipsychotic use are higher in these settings than in the community. Prior to the black-box warning, studies found that 24% to 32% of nursing home residents were treated with antipsychotics.[45-47] A study examining VA nursing homes (n = 133 facilities, n = 3,692 veterans) found that approximately 26% of residents were prescribed antipsychotics in 2004 to 2005.[48] The Center for Medicare and Medicaid Services (CMS) National Partnership to Improve Dementia Care in Nursing Homes has appeared to lower antipsychotic medication use in nursing homes; the rate decreased from 24% in long-stay nursing home residents nationwide in 2011 to 19% by the end of 2014. Specific to dementia, a 2010 CMS report[49] indicated that approximately 40% of nursing home residents with cognitive impairment and behavioral issues, without psychosis, received antipsychotics. The GAO data indicated that approximately 33% of older Medicare Part D enrollees with dementia who spent >100 days in a nursing home were prescribed an antipsychotic in 2012.[44] A recent Canadian study using drug claims data found that overall psychotropic use in patients with dementia remains high, finding that three-fourths of all patients with dementia in long-term care are given at least 1 psychotropic, and up to one-third are prescribed SGAs.[50] European data similarly show that antipsychotics continue to be prescribed to up to one-third of long-term care residents with dementia, with 7 out of 10 receiving an SGA.[1]

Table

Using antipsychotics in older patients with dementia: A summary of the evidence

Of all agents currently used for BPSD, SGAs have the strongest evidence base (from RCTs for agitation, aggression, or psychosis), although benefits are moderate at best
In terms of individual SGAs, the best evidence is for risperidone for aggression
FGAs have no clear evidence for BPSD. There may be slight benefit for haloperidol for aggression, but this medication has a higher mortality risk than SGAs
In terms of mortality risk, FGAs have a higher risk than SGAs, and SGAs have a higher risk than most other psychotropics
Individual SGAs also differ in mortality risk, with risperidone having the highest risk, followed by olanzapine, then quetiapine
Because of the nature of risk–benefit with both FGAs and SGAs in dementia, these agents should be reserved for cases where there is considerable risk of harm to self or others (eg, aggression or psychosis or after substantial efforts to utilize behavioral or environmental strategies have failed)

BPSD: behavioral and psychological symptoms of dementia; FGA: first-generation antipsychotic; RCT: randomized controlled trial; SGA: second-generation antipsychotic

Conclusions

The ***Table*** provides a summary of the evidence regarding the use of antipsychotics in patients with dementia. Expert consensus is that among BPSD, aggression and psychosis are the primary indications for using antipsychotics.[51] Based on multiple RCTs and meta-analyses, the evidence for using SGAs to treat these symptoms is moderate at best. However, in real-world practice settings, SGAs are widely used for symptoms, such as wandering, inappropriate behaviors, resistance to care, etc., for which there is *no* evidence for efficacy other than sedation. Furthermore, even when there is a potential

Clinical Point

There might be a slight benefit for haloperidol for aggression; however, it has a higher mortality risk than SGAs

Clinical Point

Among BPSD, aggression and psychosis are the primary indications for using antipsychotics

Box

Use DICE before prescribing an antipsychotic to a person with dementia

1. Describe the behavioral symptom fully (including who, what, when, and where). For example, "agitation" is not an adequate description, just as shortness of breath would not be fully descriptive to an internist. Inquire as to the degree of distress the symptom is causing the patient and caregiver.

2. Investigate the possible underlying causes of the behavior:

- person with dementia (eg, pain, infection, sensory changes, medication adverse effects)
- caregiver (eg, negative communication style, such as yelling at the person with dementia, mismatch of expectations with level of dementia)
- environment (eg, overstimulation with clutter and blaring TV).

3. Create a treatment plan to address the underlying causes found by responding to physical problems and strategizing behavioral/environmental interventions, such as:

- providing the caregiver with education/support
- enhancing the caregiver's communication with the person with dementia
- creating meaningful activities for the person with dementia
- simplifying tasks
- ensuring the environment is safe
- adjusting the stimulation in the environment (increase if under-stimulating, decrease if overstimulating).

4. Evaluate the impact of any interventions that have been implemented. If they are working, have the caregiver keep doing them. If they are ineffective, devise a new strategy.

First-line use of antipsychotics should be limited to psychosis or aggression that is causing harm or the potential for harm: significantly distressing to the person with dementia (eg, do not medicate hallucinations that are experienced as benign), impairing function (eg, not eating out of fear of being poisoned), or creating a safety risk (eg, aggression toward caregiver that is endangering their safety).

Source: Reference 51

for benefit, this must be balanced against the risk of adverse effects, including somnolence, worsened cognition, extrapyramidal symptoms, stroke, and mortality.

Clinicians who care for older adults with BPSD should strive to increase the use of first-line nonpharmacologic strategies, by using structured approaches such as **DICE** (**D**escribe, **I**nvestigate, **C**reate, **E**valuate) described in the ***Box***.[51] Antipsychotics should be reserved for situations in which nonpharmacologic approaches are unsuccessful, or there is concern for serious or imminent risk to the patient or others.

In the future, observational studies using biomarkers, such as neuroimaging markers, of brain health in older patients taking antipsychotics for various durations may give us a better understanding of long-term antipsychotic safety and tolerability and the monitoring required to assess long-term burden of specific antipsychotics in real-world samples.[52] However, because of various biases, observational data may not provide answers to all questions,[53] and a major challenge is that the number of published RCTs specific to geriatric patients is not growing substantially. Pharmacotherapy evidence is not keeping up with demographic trends. Key developments in RCTs will be the inclusion of biomarkers via neuroimaging, drug serum or brain levels, and genetic profiling. Because of the modest findings of benefits of antipsychotics in dementia and safety concerns addressing brain health in preclinical or early stages, identification of effective non-drug interventions and identifying true disease-modifying agents will be the next challenges of dementia research.

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Drug Brand Names

Chlorpromazine • Ormazine, Thorazine
Haloperidol • Haldol
Olanzapine • Zyprexa
Risperidone • Risperdal
Quetiapine • Seroquel
Valproic acid • Depakene
Ziprasidone • Geodon

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continued

Bottom Line

Second-generation antipsychotics should be prescribed for patients with behavioral and psychological symptoms of dementia only when nonpharmacological approaches are unsuccessful, or there is an imminent risk to the patient or others because of aggression or psychosis.

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Clinical Point

Potential benefits of antipsychotics must be weighed against the risk of somnolence, worsened cognition, and other adverse effects

Antipsychotics for dementia

Clinical Point

Antipsychotics should be used for dementia when nonpharmacologic strategies fail or the patient or others are at imminent risk

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