JAMA Clinical Guidelines Synopsis

Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia

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GUIDELINE TITLE Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia

DEVELOPER American Psychiatric Association (APA) Medical Specialty Society

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FUNDING SOURCE APA

TARGET POPULATIONS Individuals with dementia or neurocognitive disorders in all settings with care delivered by generalists and specialist clinicians

MAJOR RECOMMENDATIONS (1) Outside of situations when patients represent an imminent threat to themselves or others, antipsychotic medications should be used in patients with dementia for the treatment of agitation or psychosis only when symptoms are severe, are dangerous, or cause significant distress to the patient (B recommendation). (2) The clinical response to nonpharmacologic interventions should be reviewed prior to nonemergency use of an antipsychotic medication (C recommendation). (3) Pharmacologic treatment should be initiated at a low dose and titrated up to the minimum effective dose as tolerated (B recommendation). (4) If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn (B recommendation). (5) In patients who show adequate response to antipsychotic drug treatment, an attempt to taper and withdraw the drug should be made within 4 months of initiation unless a patient experienced a recurrence of symptoms with prior tapering attempts (C recommendation). (6) In patients whose antipsychotic medication is being tapered, assessment of symptoms should occur at least monthly during the taper and for at least 4 months after medication discontinuation to identify signs of recurrence and initiate a risk-benefit reassessment of treatment (C recommendation). (7) In the absence of delirium, if nonemergency antipsychotic medication treatment is indicated, haloperidol should not be used as a first-line agent (B recommendation).

Summary of the Clinical Problem

Dementia affects 5% to 16% of individuals aged 65 to 85 years in the United States and 30% to 40% of those older than 85 years.[1,2] Among individuals with dementia, psychotic symptoms are both common and troublesome. Population data suggest that 51% of patients with dementia show signs of irritability and 34% experience hallucinations.[3] Given that rates of dementia are increasing and that these symptoms can be distressing to both patients and caregivers, there is interest in and demand for effective therapies.

Characteristics of the Guideline Source

This guideline was developed by the APA.[4] The guideline writing group consisted of a chair, a vice chair, and 8 psychiatrists with research and clinical expertise. All members of the guideline writing committee were required to disclose conflicts of interest with the intent of meeting the Institute of Medicine standards. Disclosures were made before appointment, before and during the guideline development, and on publication. No other actions were taken. Experts from other disciplines were added as needed and the final group consisted of 11 members. The manuscript was reviewed by the Alzheimer Association with input also provided by members of the APA, patient and family advocacy groups, and the general public. Reviewers were asked to disclose relevant conflicts of interest (**Table**).

Evidence Base

The guideline writing group conducted literature searches in January 2013 and January 2015. The searches yielded 45 randomized clinical trials and 52 observational studies that met criteria for inclusion. Included studies were limited to those that included the second-generation antipsychotics (SGAs) olanzapine, risperidone, quetiapine, and aripiprazole. There is no relevant information in the literature on asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, paliperidone, or ziprasidone. The strength

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Fair
Clinical practice guideline-systemic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

of the evidence was evaluated for risk of bias, consistency of findings across studies, directness of the effect on a specific health outcome, and precision of the estimate of effect using the Agency for Healthcare Research and Quality 2014 recommendations.[5] The recommendations' strengths were rated by the guideline writing group. Fifteen recommendations were made in the guideline, 7 of which are included herein. No recommendations received an A rating. Five recommendations, 4 of which are discussed herein, received a B rating. Three C-rating recommendations are also included in this review.

The best evidence for use of SGAs is for agitation. This evidence is primarily from studies using risperidone. The evidence for use of SGAs in psychosis suggests low utility (low strength of evidence for a very small effect). The evidence for risperidone is substantially better than for the rest of the SGAs for this indication (moderate strength of evidence for a small effect). As a point of reference, the standardized mean differences in the studies considered ranged from −0.11 to 0.38, with most estimates in the 0.3 to 0.4 range. The evidence of efficacy for SGAs in the management of overall behavioral/psychological symptoms also suggests low utility (high strength of evidence for a very small effect). For this indication, the evidence for aripiprazole is substantially better than for other SGAs, with moderate strength of evidence for a small effect.

A number of studies have assessed the effects of discontinuing treatment. In a meta-analysis, individuals randomized to receive placebo (vs continued antipsychotic therapy) had a higher likelihood of symptom recurrence. Individuals who had higher baseline levels of symptoms or who were taking higher doses of antipsychotics were more likely to have a recurrence of symptoms with discontinuation.[6] There are no published studies on the optimal duration of antipsychotic treatment in individuals with dementia.

Adverse effects of first-generation antipsychotics (FGAs), including increased mortality vs SGAs, led to the recommendation that haloperidol not be a first-line medication for patients with dementia. Haloperidol is specifically mentioned in the guidelines rather than the class of FGAs because most studies used haloperidol as the FGA. There is no reason to believe that other FGAs would be safer. First-generation antipsychotics might be considered for short-term use in individuals with delirium given haloperidol's rapid onset and its availability in intravenous and intramuscular preparations.

Benefits and Harms

Following the proper assessment of agitation and psychosis, including consideration of specific causative factors and the effect of nonpharmacologic interventions, SGAs are associated with benefits including reductions of agitation and aggression, alleviation of depression, improvement in sleep, and increase in productive activity.

The potential for harm from antipsychotics is significant. Typical problems associated with antipsychotics include metabolic disorders like weight gain and increased risk of diabetes, falls, sedation, extrapyramidal effects, dystonia, and movement disorders. There is also increased risk of mortality, estimated to be as high as an absolute increase of 1.2% (relative risk, 1.65; 95% CI, 1.19-2.29) in one meta-analysis.[7,8]

Discussion

As the population of the United States ages, the number of individuals with dementia will increase. This is the first comprehensive guideline for the assessment and treatment of some of the more challenging aspects of dementia: psychosis, agitation, and aggression. However, the recommended treatments are only minimally effective, as evidenced by their rather small effect sizes.

Areas in Need of Further Study or Ongoing Research

This guideline references the trials of nonpharmacologic and pharmacologic interventions for treatment of agitation and psychosis in patients with dementia. Further study of these interventions will clarify the appropriate means of treating these clinical issues. Considering the small effect sizes of these interventions, new therapies need to be developed for these indications. Ultimately, the most effective therapy would be interventions to reduce the development of dementia.

Related guidelines and other resources

Guidelines for the management of cognitive and behavioral problems in dementia. *J Am Board Fam Med*. doi:10.3122/jabfm.2012.03.100183

A consensus guideline for antipsychotic drug use for dementia in care homes. *Int Psychogeriatr*. doi:10.1017/S1041610215000745

ARTICLE INFORMATION

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