

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia

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At its December 2015 meeting, The APA Board of Trustees approved the APA Practice Guideline Writing Group's "Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia." [The full guideline is available at <http://psychiatryonline.org/doi/book/10.1176/appi.books.9780890426807>]

INTRODUCTION

The goal of this guideline is to improve the care of patients with dementia who are exhibiting agitation or psychosis. More specifically, this guideline focuses on the judicious use of antipsychotic medications when agitation or psychosis occurs in association with dementia and does not review evidence for or focus on other pharmacological interventions. The guideline is intended to apply to individuals with dementia in all settings of care as well as to care delivered by generalist and specialist clinicians. Recommendations regarding treatment with antipsychotic medications are not intended to apply to individuals who are receiving antipsychotic medication for another indication (e.g., chronic psychotic illness) or individuals who are receiving an antipsychotic medication in an urgent context.

Expert consensus suggests that use of an antipsychotic medication in individuals with dementia can be appropriate, particularly in individuals with dangerous agitation or psychosis, and can minimize the risk of violence, reduce patient distress, improve patient's quality of life, and reduce caregiver burden. However, in clinical trials, the benefits of antipsychotic medications are at best small (Corbett et al., 2014; Kales et al., 2015) whether assessed through placebo-controlled trials, head-to-head comparison trials, or discontinuation trials. There is also consistent evidence that antipsychotics are associated with clinically significant adverse effects, including mortality. Consequently, decisions about the treatment of psychosis or agitation in an individual with dementia will be an outgrowth of the initial assessment and an understanding of the goals and preferences of the patient (if clinically feasible) and the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. Such decisions will also need to balance the potential benefits and harms of a particular

intervention as compared to other therapeutic options for the individual patient. The full text of the practice guideline includes a detailed description of expert consensus findings and research evidence related to effects of antipsychotic medication in individuals with dementia. It also describes aspects of guideline implementation that are relevant to individual patients' circumstances and clinical presentation.

Overview of the Development Process

Since the 2011 publication of the Institute of Medicine report, *Clinical Practice Guidelines We Can Trust*, there has been an increasing focus on using clearly defined, transparent processes for rating the quality of evidence and the strength of the overall body of evidence in systematic reviews of the scientific literature. This guideline was developed using a process intended to be consistent with the recommendations of the Institute of Medicine (2011), the Principles for the Development of Specialty Society Clinical Guidelines of the Council of Medical Specialty Societies (2012) and the requirements of the Agency for Healthcare Research and Quality (AHRQ) for inclusion of a guideline in the National Guidelines Clearinghouse. Parameters used for the guidelines' systematic review are included with the full text of the guideline; the development process is fully described in the following document available on the American Psychiatric Association (APA) website: <http://www.psychiatry.org/File%20Library/Psychiatrists/Practice/Clinical%20Practice%20Guidelines/Guideline-Development-Process.pdf>. To supplement the expertise of members of the guideline work group, we used a "snowball" survey methodology (Yager 2014) to identify experts on the treatment of agitation or psychosis in individuals with dementia. Results of this expert survey are included in the Appendix of the full practice guideline.

Rating the Strength of Research Evidence and Recommendations

The guideline recommendations are rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation), which is used by multiple professional organizations around the world to develop practice guideline recommendations

(Guyatt et al., 2013). With the GRADE approach, the strength of a guideline statement reflects the level of confidence that potential benefits of an intervention outweigh the potential harms (Andrews et al., 2013). This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. Evidence for the benefit of a particular intervention within a specific clinical context is identified through systematic review and is then balanced against the evidence for harms. In this regard, harms are broadly defined and might include direct and indirect costs of the intervention (including opportunity costs) as well as potential for adverse effects from the intervention. Whenever possible, we have followed the admonition to current guideline development groups to avoid using words such as “might” or “consider” in drafting these recommendations as they can be difficult for clinicians to interpret (Shiffman et al., 2005).

As described under Guideline Development Process, each final rating is a consensus judgment of the authors of the guideline and is endorsed by the APA Board of Trustees. A “recommendation” (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. A “suggestion” (denoted by the numeral 2 after the guideline statement) indicates uncertainty (i.e., the balance of benefits and harms is difficult to judge, or either the benefits or the harms are unclear). Each guideline statement also has an associated rating for the “strength of supporting research evidence.” Three ratings are used—high, moderate, and low (denoted by the letters A, B, and C, respectively)—and reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect on a specific health outcome, and precision of the estimate of effect and risk of bias in available studies (Agency for Healthcare Research and Quality 2014; Balshem et al., 2011; Guyatt et al., 2006).

It is well recognized that there are guideline topics and clinical circumstances for which high quality evidence from clinical trials is not possible or is unethical to obtain (Council of Medical Specialty Societies, 2012). For example, many questions need to be asked as part of an assessment and inquiring about a particular symptom or element of the history cannot be separated out for study as a discrete intervention. It would also be impossible to separate changes in outcome due to assessment from changes in outcomes due to ensuing treatment. Research on psychiatric assessments and some psychiatric interventions can also be complicated by multiple confounding factors such as the interaction between the clinician and the patient or the patient’s unique circumstances and experiences. For these and other reasons, many topics covered in this guideline have relied on forms of evidence such as consensus opinions of experienced clinicians or indirect findings from observational studies rather than being based on research from randomized trials. The GRADE working group and guidelines developed by other professional organizations have noted that a strong recommendation may be appropriate even in the absence of research evidence when

sensible alternatives do not exist (Andrews et al., 2013; Brito et al., 2013; Djulbegovic et al., 2009; Hazlehurst et al., 2013).

Proper Use of Guidelines

The APA Practice Guidelines are assessments of current scientific and clinical information provided as an educational service. The guidelines 1) should not be considered as a statement of the standard of care or inclusive of all proper treatments or methods of care; 2) are not continually updated and may not reflect the most recent evidence, as new evidence may emerge between the time information is developed and when the guidelines are published or read; 3) address only the question(s) or issue(s) specifically identified; 4) do not mandate any particular course of medical care; 5) are not intended to substitute for the independent professional judgment of the treating provider; and 6) do not account for individual variation among patients. As such, it is not possible to draw conclusions about the effects of omitting a particular recommendation, either in general or for a specific patient. Furthermore, adherence to these guidelines will not ensure a successful outcome for every individual, nor should these guidelines be interpreted as including all proper methods of evaluation and care or excluding other acceptable methods of evaluation and care aimed at the same results. The ultimate recommendation regarding a particular assessment, clinical procedure, or treatment plan must be made by the clinician in light of the psychiatric evaluation, other clinical data, and the diagnostic and treatment options available. Such recommendations should be made in collaboration with the patient, whenever possible, and incorporate the patient’s personal and sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes. For all of these reasons, APA cautions against the use of guidelines in litigation. Use of these guidelines is voluntary. APA provides the guidelines on an “as is” basis, and makes no warranty, expressed or implied, regarding them. APA assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the guidelines or for any errors or omissions.

GUIDELINE STATEMENTS

Assessment of Behavioral/Psychological Symptoms of Dementia

Statement 1. APA recommends that patients with dementia¹ be assessed for the type, frequency, severity, pattern, and timing of symptoms. (1C)

Statement 2. APA recommends that patients with dementia be assessed for pain and other potentially modifiable contributors to symptoms as well as for factors, such as the subtype of dementia, that may influence choices of treatment. (1C)

¹Throughout this guideline, we use the term *dementia*, which was used in the evidence that was considered in developing these recommendations. These recommendations are also meant to apply to individuals with major neurocognitive disorder, as defined in the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* (DSM–5).

Statement 3. APA recommends that in patients with dementia with agitation or psychosis, response to treatment be assessed with a quantitative measure. (1C)

Development of a Comprehensive Treatment Plan

Statement 4. APA recommends that patients with dementia have a documented comprehensive treatment plan that includes appropriate person-centered nonpharmacological and pharmacological interventions, as indicated. (1C)

Assessment of Benefits and Risks of Antipsychotic Treatment for the Patient

Statement 5. APA recommends that nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient. (1B)

Statement 6. APA recommends reviewing the clinical response to nonpharmacological interventions prior to non-emergency use of an antipsychotic medication to treat agitation or psychosis in patients with dementia. (1C)

Statement 7. APA recommends that before nonemergency treatment with an antipsychotic is initiated in patients with dementia, the potential risks and benefits from antipsychotic medication be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. (1C)

Dosing, Duration and Monitoring of Antipsychotic Treatment

Statement 8. APA recommends that if a risk/benefit assessment favors the use of an antipsychotic for behavioral/psychological symptoms in patients with dementia, treatment should be initiated at a low dose to be titrated up to the minimum effective dose as tolerated. (1B)

Statement 9. APA recommends that if a patient with dementia experiences a clinically significant side effect of antipsychotic treatment, the potential risks and benefits of antipsychotic medication should be reviewed by the clinician to determine if tapering and discontinuing of the medication is indicated. (1C)

Statement 10. APA recommends that in patients with dementia with agitation or psychosis, 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. (1B)

Statement 11. APA recommends that in a patient who has shown a positive response to treatment, decision making about possible tapering of antipsychotic medication should be accompanied by a discussion with the patient (if clinically feasible) as well as with the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. The aim of such a discussion is to elicit their preferences and concerns and to review the initial goals, observed benefits and side effects of antipsychotic treatment, and potential risks of continued exposure to antipsychotics,

as well as past experience with antipsychotic medication trials and tapering attempts. (1C)

Statement 12. APA recommends that in patients with dementia who show adequate response of behavioral/psychological symptoms to treatment with an antipsychotic drug, an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication. (1C)

Statement 13. APA recommends that in patients with dementia 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 trigger a reassessment of the benefits and risks of antipsychotic treatment. (1C)

Use of Specific Antipsychotic Medications, Depending on Clinical Context

Statement 14. APA recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is indicated, haloperidol should not be used as a first-line agent. (1B)

Statement 15. APA recommends that in patients with dementia with agitation or psychosis, a long-acting injectable antipsychotic medication should not be utilized unless it is otherwise indicated for a co-occurring chronic psychotic disorder. (1B)

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REFERENCES

- Agency for Healthcare Research and Quality: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD, Agency for Healthcare Research and Quality. January 2014. Available at: <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318>
- Andrews JC, Schünemann HJ, Oxman AD, et al: GRADE guidelines: 15. Going from evidence to recommendation: determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013; 66(7):726–735
- Balshem H, Helfand M, Schünemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64(4):401–406
- Brito JP, Domecq JP, Murad MH, et al: The Endocrine Society guidelines: when the confidence cart goes before the evidence horse. *J Clin Endocrinol Metab* 2013; 98(8):3246–3252

- Corbett A, Burns A, Ballard C: Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. *BMJ* 2014; 349:g6420
- Council of Medical Specialty Societies (CMSS): Principles for the Development of Specialty Society Clinical Guidelines. Chicago, IL, Council of Medical Specialty Societies, 2012
- Djulfbegovic B, Trikalinos TA, Roback J, et al: Impact of quality of evidence on the strength of recommendations: an empirical study. *BMC Health Serv Res* 2009; 9:120
- Guyatt G, Eikelboom JW, Akl EA, et al: A guide to GRADE guidelines for the readers of JTH. *J Thromb Haemost* 2013; 11(8):1603–1608
- Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; 129(1):174–181
- Hazlehurst JM, Armstrong MJ, Sherlock M, et al: A comparative quality assessment of evidence-based clinical guidelines in endocrinology. *Clin Endocrinol (Oxf)* 2013; 78(2):183–190
- Kales HC, Gitlin LN, Lyketsos CG: Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015; 350:h369
- Shiffman RN, Dixon J, Brandt C, et al: The GuideLine Implementability Appraisal (GLIA): development of an instrument to identify obstacles to guideline implementation. *BMC Med Inform Decis Mak* 2005; 5:23
- Yager J, Kunkle R, Fochtmann LJ, et al: Who's your expert? Use of an expert opinion survey to inform development of American Psychiatric Association practice guidelines. *Acad Psychiatry* 2014; 38(3):376–382