The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia

George A. Keepers, M.D., (Chair), Laura J. Fochtmann, M.D., M.B.I., (Vice-Chair; Methodologist), Joan M. Anzia, M.D., Sheldon Benjamin, M.D., Jeffrey M. Lyness, M.D., Ramin Mojtabai, M.D., Mark Servis, M.D., Art Walaszek, M.D., Peter Buckley, M.D., Mark F. Lenzenweger, Ph.D., Alexander S. Young, M.D., M.S.H.S., Amanda Degenhardt, M.D., Seung-Hee Hong (Systematic Review)

At its December 2019 meeting, the American Psychiatric Association (APA) Board of Trustees approved "The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia." The full guideline is available at APA's Practice Guidelines website.

INTRODUCTION

The goal of this guideline is to improve the quality of care and treatment outcomes for patients with schizophrenia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (American Psychiatric Association 2013). Since publication of the last full practice guideline (American Psychiatric Association 2004) and guideline watch (American Psychiatric Association 2009) on schizophrenia, there have been many studies on new pharmacological and nonpharmacological treatments for schizophrenia. Additional research has expanded our knowledge of previously available treatments. The guideline focuses specifically on evidence-based pharmacological and nonpharmacological treatments for schizophrenia but also includes statements related to assessment and treatment planning that are an integral part of patient-centered care (Box 1).

Worldwide, schizophrenia is one of the top 20 causes of disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). The lifetime prevalence of schizophrenia is estimated to be approximately 0.7% (McGrath et al. 2008; Moreno-Küstner et al. 2018; van der Werf et al. 2014), although findings vary depending on the study location, demographic characteristics of the sample, the approach used for case-finding, the method used for diagnostic confirmation, and the diagnostic criteria used. Economic burdens associated with schizophrenia are high (Chapel et al. 2017; Jin and Mosweu 2017), with an estimated cost of more than $150 billion annually in the United States based on 2013 data (Cloutier et al. 2016). Schizophrenia is also associated with increased mortality, with a shortened lifespan and standardized mortality ratios that are reported to be twofold to fourfold those in the general population (Hayes et al. 2017; Heilä et al. 2005; Hjorthøj et al. 2017; Laursen et al. 2014; Lee et al. 2018; Oakley et al. 2018; Olfson et al. 2015; Tanskanen et al. 2018; Walker et al. 2015). The common co-occurrence of other psychiatric disorders (Plana-Ripoll et al. 2019), including substance use disorders (Hunt et al. 2018), contributes to morbidity and mortality among individuals with schizophrenia. About 4%–10% of persons with schizophrenia die by suicide, with rates that are highest among males in the early course of the disorder (Drake et al. 1985; Heilä et al. 2005; Hor and Taylor 2010; Inskip et al. 1998; Laursen et al. 2014; Nordentoft et al. 2011; Palmer et al. 2005; Popovic et al. 2014; Saha et al. 2007; Tanskanen et al. 2018). Increases in morbidity and mortality related to physical health in individuals with schizophrenia are likely associated with such factors as obesity, diabetes, hyperlipidemia, greater use of cigarettes, reduced engagement in health maintenance (e.g. diet, exercise), and disparities in access to preventive health care and treatment for physical conditions (Bergamo et al. 2014; De Hert et al. 2011; Druss et al. 2000; Janssen et al. 2015; Kisely et al. 2007, 2013; Kugathasan et al. 2018; Lawrence et al. 2010; Moore et al. 2015). Lack of access to adequate psychiatric treatment may also influence mortality (Schoenbaum et al. 2017). Accordingly, the overall goal of this guideline is to enhance the treatment of schizophrenia for affected individuals, thereby reducing the mortality, morbidity, and significant psychosocial and health consequences of this important psychiatric condition.

OVERVIEW OF THE DEVELOPMENT PROCESS

Since the publication of the Institute of Medicine (now known as National Academy of Medicine) report, *Clinical Practice Guidelines We Can Trust* (Institute of Medicine 2011), 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) and the *Principles for the Development of Specialty Society Clinical Guidelines* of the Council of Medical Specialty Societies (2012). Parameters used for the guideline's systematic review are included with the full text of the guideline. The APA

BOX 1. Guideline Statements[a]

Assessment and Determination of Treatment Plan

1. APA *recommends* **(1C)** that the initial assessment of a patient with a possible psychotic disorder include the reason the individual is presenting for evaluation; the patient's goals and preferences for treatment; a review of psychiatric symptoms and trauma history; an assessment of tobacco use and other substance use; a psychiatric treatment history; an assessment of physical health; an assessment of psychosocial and cultural factors; a mental status examination, including cognitive assessment; and an assessment of risk of suicide and aggressive behaviors, as outlined in APA's *Practice Guidelines for the Psychiatric Evaluation of Adults* (3rd edition).
2. APA *recommends* **(1C)** that the initial psychiatric evaluation of a patient with a possible psychotic disorder include a quantitative measure to identify and determine the severity of symptoms and impairments of functioning that may be a focus of treatment.
3. APA *recommends* **(1C)** that patients with schizophrenia have a documented, comprehensive, and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Pharmacotherapy

4. APA *recommends* **(1A)** that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.*
5. APA *recommends* **(1A)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.*
6. APA *suggests* **(2B)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.*
7. APA *recommends* **(1B)** that patients with treatment-resistant schizophrenia be treated with clozapine. *
8. APA *recommends* **(1B)** that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*
9. APA *suggests* **(2C)** that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.*
10. APA *suggests* **(2B)** that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*
11. APA *recommends* **(1C)** that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.
12. APA *suggests* **(2C)** the following options for patients who have parkinsonism associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.
13. APA *suggests* **(2C)** the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.
14. APA *recommends* **(1B)** that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).

Psychosocial Intervention

15. APA *recommends* **(1B)** that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.*
16. APA *recommends* **(1B)** that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis (CBTp).*
17. APA *recommends* **(1B)** that patients with schizophrenia receive psychoeducation.*
18. APA *recommends* **(1B)** that patients with schizophrenia receive supported employment services.*
19. APA *recommends* **(1B)** that patients with schizophrenia receive assertive community treatment if there is a history of poor engagement with services leading to frequent relapse or social disruption (e.g. homelessness; legal difficulties, including imprisonment).*
20. APA *suggests* **(2B)** that patients with schizophrenia who have ongoing contact with family receive family interventions.*
21. APA *suggests* **(2C)** that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*
22. APA *suggests* **(2C)** that patients with schizophrenia receive cognitive remediation.*
23. APA *suggests* **(2C)** that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*
24. APA *suggests* **(2C)** that patients with schizophrenia be treated with supportive psychotherapy.*

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[a] Each statement includes a number rating that reflects the confidence in the statement: 1=Recommendation, indicating benefits of the intervention clearly outweigh harms; 2=Suggestion, indicating balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made. Each statement also has a letter rating for the strength of supporting research evidence (A=high; B=moderate; C=low), which 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, precision of the estimate of effect, and risk of bias in available studies.

*This guideline statement should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.

website features a full description of the guideline development process.

RATING THE STRENGTH OF RESEARCH EVIDENCE AND RECOMMENDATIONS

Development of guideline statements entails weighing the potential benefits and harms of each statement and then identifying the level of confidence in that determination. This concept of balancing benefits and harms to determine guideline recommendations and strength of recommendations is a hallmark of Grading of Recommendations Assessment, Development and Evaluation (GRADE), which is used by multiple professional organizations around the world to develop practice guideline recommendations (Guyatt et al. 2013). With the GRADE approach, recommendations are rated by assessing the confidence that the benefits of the statement outweigh the harms and burdens of the statement, determining the confidence in estimates of effect as reflected by the quality of evidence, estimating patient values and preferences (including whether they are similar across the patient population), and identifying whether resource expenditures are worth the expected net benefit of following the recommendation (Andrews et al. 2013).

In weighing the balance of benefits and harms for each statement in this guideline, our 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 events from the intervention.

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 research from randomized trials. 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). The GRADE working group and guidelines developed by other professional organizations have noted that a strong recommendation or "good practice statement" 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). For each guideline statement, we have described the type and strength of the available evidence that was available as well as the factors, including patient preferences, that were used in determining the balance of benefits and harms.

The authors of the guideline determined each final rating following parameters set forth in the "Guideline Development Process" 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 greater uncertainty: although the benefits of the statement are still viewed as outweighing the harms, the balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made. Each guideline statement also has an associated rating for the strength of supporting research evidence. Three ratings are used: *high*, *moderate*, or *low* (denoted by the letters A, B, and C, respectively). These ratings 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, 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).

GUIDELINE SCOPE

The scope of this practice guideline is shaped by the *Treatments for Schizophrenia in Adults* (McDonagh et al. 2017), a systematic review that was commissioned by the Agency for Healthcare Research and Quality (AHRQ) and that serves as a principal source of information for the guideline. The AHRQ review uses the DSM-5 definition of schizophrenia; however, many of the systematic reviews included studies that used earlier DSM or International Classification of Disease criteria for schizophrenia. Several studies, particularly those assessing harms and psychosocial interventions, also included patients with a schizophrenia spectrum disorder diagnosis. Consequently, discussion of treatment, particularly treatment of first-episode psychosis, may also be relevant to individuals with schizophreniform disorder.

Although many of the studies included in the systematic review also included individuals with a diagnosis of schizoaffective disorder, these data were rarely analyzed separately in a way that would permit unique recommendations to be crafted for this group of patients. In addition, this guideline does not address issues related to identification or treatment of attenuated psychosis syndrome or related syndromes of high psychosis risk, which were not part of the AHRQ systematic review. Data are also limited on individuals with schizophrenia and significant physical health conditions or co-occurring psychiatric conditions, including substance use disorders. Nevertheless, in the absence of more robust evidence, the statements in this guideline should generally be applicable to individuals with co-occurring conditions, including individuals who receive treatment using integrated collaborative care or inpatient or outpatient medical settings. Although treatment-related costs are often barriers to receiving treatment and cost-effectiveness considerations are relevant to health care policy, cost-effectiveness

considerations are outside the scope of this guideline and its recommendations.

The full text of the practice guideline includes a detailed description of research evidence related to the effects of pharmacological and nonpharmacological treatments in individuals with schizophrenia. It also describes aspects of guideline implementation that are relevant to individual patients' circumstances and preferences.

AUTHOR AND ARTICLE INFORMATION

APA Practice Guideline Writing Group (George A. Keepers, M.D., Chair).

Address correspondence to Jennifer Medicus (jmedicus@psych.org).

APA wishes to acknowledge the contributions of APA staff and former staff (Jennifer Medicus, Seung-Hee Hong, Samantha Shugarman, Michelle Dirst, Kristin Kroeger Ptakowski). APA also wishes to acknowledge the contribution of Amanda S. Eloma, Pharm.D, BCPP, in reviewing information related to medications in the guideline and associated tables. In addition, APA and the Guideline Writing Group especially thank Laura J. Fochtmann, M.D., M.B.I., Seung-Hee Hong, and Jennifer Medicus for their outstanding work and effort in developing this guideline. APA also thanks the APA Committee on Practice Guidelines (Daniel J. Anzia, M.D., Chair), liaisons from the APA Assembly for their input and assistance, and APA Councils and others for providing feedback during the comment period.

Am J Psychiatry 2020; 177:868–872; doi: 10.1176/appi.ajp.2020.177901

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