THE AMERICAN PSYCHIATRIC ASSOCIATION
PRACTICE GUIDELINE FOR THE TREATMENT
OF PATIENTS WITH SCHIZOPHRENIA

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<td>2. AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<td>3. AIMS</td>
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<td>4. APA</td>
<td>American Psychiatric Association</td>
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<td>5. ANC</td>
<td>Absolute neutrophil counts</td>
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<td>6. BAP</td>
<td>British Association for Psychopharmacology</td>
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<td>7. BMI</td>
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<td>Brief Psychiatric Rating Scale</td>
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<td>11. CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>12. CGI</td>
<td>Clinical Global Impression</td>
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<td>13. CI</td>
<td>Confidence interval</td>
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<td>cytochrome P450</td>
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<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>18. DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th Edition</td>
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<td>19. ECG</td>
<td>Electrocardiography</td>
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<td>21. ER</td>
<td>Extended release</td>
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<td>22. FDA</td>
<td>U.S. Food and Drug Administration</td>
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<td>23. FGA</td>
<td>First-generation antipsychotic</td>
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<td>Global Assessment of Functioning</td>
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<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<td>26. HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
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<td>27. HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>28. HR</td>
<td>Hazard ratio</td>
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<td>29. ICD</td>
<td>International Classification of Disease</td>
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<td>30. IPS</td>
<td>individual placement and support</td>
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<td>31. LAI</td>
<td>Long-acting injectable</td>
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<td>32. MD</td>
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<td>33. NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>34. NMS</td>
<td>Neuroleptic malignant syndrome</td>
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<td>41. PORT</td>
<td>Schizophrenia Patient Outcomes Research Team</td>
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56 RAISE Recovery After Initial Schizophrenia Episode
58 RANZCP Royal Australian and New Zealand College of Psychiatry
60 RCT Randomized controlled trial
61 REMS Risk Evaluation and Mitigation Strategy
62 RR Risk ratio or relative risk
63 SANS Assessment of Negative Symptoms
64 SAPS Scale for the Assessment of Positive Symptoms
65 SFS Social Functioning Scale
66 SD Standard deviation
68 SGA Second-generation antipsychotic
69 SIGN Scottish Intercollegiate Guidelines Network
71 SMD Standardized mean difference
72 SOE Strength of evidence
73 SOFAS Social and Occupational Functioning Assessment Scale
75 TdP torsades de pointes
76 TMS Transcranial magnetic stimulation
77 TRRIP Treatment Response and Resistance in Psychosis
79 VMAT2 Vesicular monoamine transporter2
80 WFSBP World Federation of Societies of Biological Psychiatry
82 WHODAS 2.0 World Health Organization Disability Schedule 2.0
84 WHOQOL-BREF World Health Organization Quality of Life scale
86 WMD Weighted mean difference
Introduction

Rationale

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* (DSM-5; American Psychiatric Association 2013a). Since publication of the last American Psychiatric Association (APA) practice guideline (American Psychiatric Association 2004) and guideline watch on schizophrenia (American Psychiatric Association 2009), there have been many studies on new pharmacological and non-pharmacological treatments for schizophrenia. Additional research has expanded our knowledge of previously available treatments. This practice guideline aims to help clinicians optimize care for their patients by providing evidence-based statements that are intended to enhance knowledge and increase the appropriate use of treatments for schizophrenia.

Schizophrenia is associated with significant health, social, occupational, and economic burdens as a result of its early onset, and its severe and often persistent symptoms (American Psychiatric Association 2013a). Worldwide, schizophrenia is one of the top 20 causes of disability (GBD 2017; Disease and Injury Incidence and Prevalence Collaborators 2018). Economic burdens associated with schizophrenia are high (Chapel et al. 2017; Jin and Mosweu 2017), with an estimated cost of over $150 billion annually in the United States based on 2013 data (Cloutier et al. 2016). Lost productivity due to unemployment and caregiving each account for approximately one-third of total costs, and direct health care costs account for approximately one-quarter of total costs. The lifetime prevalence of schizophrenia is estimated to be approximately 0.7% (McGrath et al. 2008; Moreno-Küstner et al. 2008; van der Werf et al. 2014), although findings vary depending upon 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.

Schizophrenia is also associated with increased mortality, with a shortened lifespan and standardized mortality ratios that are reported to be two to four-fold 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, particularly 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). Additional causes of death also include other unnatural causes, such as accidents and traumatic injuries, and physical conditions, such as cardiovascular, respiratory, and infectious diseases (American Psychiatric Association 2013a; 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). Increases in morbidity and mortality related to physical health in individuals with schizophrenia are likely associated with factors such 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
This practice guideline focuses on evidence-based pharmacological and non-pharmacological treatments for schizophrenia. In addition, it also includes statements related to assessment and treatment planning, which are an integral part of patient-centered care. Thus, 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.

Scope of Document

The scope of this document is shaped by the systematic review on *Treatments for Schizophrenia in Adults* (McDonagh et al. 2017), which was commissioned by The Agency for Healthcare Research and Quality (AHRQ) and serves as a principal source of information for this 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 (ICD) criteria of schizophrenia. Several studies, particularly for assessing harms and psychosocial interventions, also included patients with a schizophrenia spectrum disorder diagnosis.

The statements in this guideline will be relevant to individuals with schizophrenia. Discussion of the treatment, particularly treatment of first-episode psychosis, will 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. Data is also limited on individuals with schizophrenia and significant physical health conditions or co-occurring psychiatric conditions, including substance use disorders. Many of the available studies excluded these individuals from the clinical trial or did not analyze data separately for these patient subgroups. Nevertheless, in the absence of more robust evidence, the statements in this guideline should generally be applicable to individuals with co-occurring conditions.

Although treatment related costs are often barriers to receiving treatment and cost-effectiveness considerations are relevant to health care policy, few high-quality studies exist on the cost effectiveness of treatments for schizophrenia. In addition, costs of treatment typically differ by country and geographic region and vary widely with the health system and payment model. Consequently, cost-effectiveness considerations were outside the scope of this guideline and its recommendations.

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 (Institute of Medicine 2011), *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 development process is fully described in the following document available at the APA Web site: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines/guideline-development-process.

Rating the Strengths of Guideline Statements and Supporting Research Evidence

Development of guideline statements entails weighing the potential benefits and harms of the 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 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, 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 may include serious adverse events, less serious adverse events that affect tolerability, minor adverse events, negative effects of the intervention on quality of life, barriers and inconveniences associated with treatment, direct and indirect costs of the intervention (including opportunity costs), and other negative aspects of the treatment that may influence decision making by the patient, the clinician, or both.

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). 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 outcomes 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. 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
The authors of the guideline determined each final rating, as described in the section “Guideline Development Process” that 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 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 either 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, 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, 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).

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, the 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 Statement Summary

Assessment and 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, a review of psychiatric symptoms and trauma history, a substance use assessment, a psychiatric treatment history, an assessment of physical health, an assessment of psychosocial and cultural factors, 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 symptoms that may be the focus of treatment and to determine their severity.

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 (1B) that patients with treatment-resistant schizophrenia be treated with clozapine. *

6. APA recommends (1B) that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*

7. APA suggests (2C) that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.*

8. APA recommends (1A) that patients with schizophrenia whose symptoms have improved with antipsychotic medication continue to be treated with an antipsychotic medication.*

9. APA suggests (2B) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.*

10. APA recommends (1C) that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.

11. 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.

12. 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.

13. 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 transporter2 (VMAT2) (e.g., deutetrabenazine, tetrabenazine, valbenazine).

Psychosocial Interventions
14. APA recommends (1B) that patients with schizophrenia be treated with cognitive-behavioral therapy (CBT).*

15. APA recommends (1B) that patients with schizophrenia receive psychoeducation.*

16. APA recommends (1B) that patients with schizophrenia receive supported employment services.*

17. 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).*

18. APA recommends (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a team-based, multicomponent program.*

19. APA suggests (2C) that patients with schizophrenia receive cognitive remediation.*

20. APA suggests (2C) that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*

21. APA suggests (2C) that patients with schizophrenia be treated with supportive psychotherapy.*

22. APA suggests (2B) that patients with schizophrenia who have ongoing contact with family receive family interventions.*

23. APA suggests (2C) that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*

*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.
Guideline Statements and Implementation

Assessment and Determination of Treatment Plan

Statement 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, a review of psychiatric symptoms and trauma history, a substance use assessment, a psychiatric treatment history, an assessment of physical health, an assessment of psychosocial and cultural factors, 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).*

Implementation

The importance of the psychiatric evaluation cannot be underestimated because it serves as the initial basis for a therapeutic relationship with the patient and provides information that is crucial to differential diagnosis, shared decision making about treatment, and educating patients and family members about factors such as illness course and prognosis.

APA's Practice Guidelines for the Psychiatric Evaluation of Adults, 3rd edition (American Psychiatric Association 2016) describes recommended and suggested elements of assessment for any individual who presents with psychiatric symptoms. (See Table 1). These elements are by no means comprehensive and additional areas of inquiry will become apparent as the evaluation unfolds, depending upon the responses to initial questions, the presenting concerns, the observations of the clinician during the assessment, the complexity and urgency of clinical decision making, and other aspects of the clinical context. Other aspects of the mental status examination will also be important to assess. For example, a detailed inquiry into hallucinations and delusions will often identify psychotic experiences in addition to the presenting concerns and inquiring about the patient’s degree of insight and judgment will provide information relevant to risk assessment and treatment adherence. In many circumstances, aspects of the evaluation will extend across multiple visits (American Psychiatric Association 2016).

The specific approach to the interview will depend on many factors, including the patient’s ability to communicate, degree of cooperation, illness severity, and ability to recall historical details (American Psychiatric Association 2016). Factors such as the patient’s health literacy (Clausen et al. 2016) and cultural background (Lewis-Fernández et al. 2016) can also influence the patient’s understanding or interpretation of questions. Typically, a psychiatric evaluation involves a direct interview between the patient and the clinician (American Psychiatric Association 2016). The use of open-ended empathic questions about the patient’s current life circumstances and reasons for evaluation can provide an initial picture of the individual and serve as a way of establishing rapport. Such questions can be followed up with additional structured inquiry about history, symptoms, or observations made during the assessment. Patients may also be asked to complete electronic- or paper-based forms that ask about

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* 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.
psychiatric symptoms or key aspects of the patient’s history (American Psychiatric Association 2016). When available, prior medical records, electronic prescription databases, and input from other treating clinicians can add further details to the history or corroborate information obtained in the interview (American Psychiatric Association 2016).

Family members, friends, and other individuals involved in the patient’s support network can be an important part of the patient’s care team and valuable sources of collateral information about the reason for evaluation, the patient’s past history, and current symptoms and behavior (American Psychiatric Association 2016). Outreach to family, friends, and others in the support network will typically occur with the patient’s permission. In situations in which the patient is given the opportunity and does not object, necessary information can be shared with family members or other persons involved in the patient’s care or payment for care (United States Department of Health and Human Services; Office for Civil Rights 2017b). For example, if a relative is present with the patient at an appointment, the clinician may discuss information about medications or give education about warning signs of a developing emergency. In some instances, however, patients may ask that family or others not be contacted. When this is the case, the patient can usually identify someone who they trust to provide additional information and they are often willing to reconsider contact as treatment proceeds. It is also useful to discuss the reasons that the patient has concerns about contacts with family members or other important people in the patient’s life. For example, a patient may wish to avoid burdening a loved one, may have felt unsupported by a particular family member in the past, or may be experiencing delusional beliefs that involve a family member or friend. He or she may also want to limit the information that clinicians receive about past or recent treatment, symptoms, or behaviors. Even when a patient does not want a specific person to be contacted, the clinician may listen to information provided by that individual, as long as confidential information is not provided to the informant (American Psychiatric Association 2016). Also, to prevent or lessen a serious and imminent threat to the health or safety of the patient or others, the Principles of Medical Ethics (American Psychiatric Association 2013f) and the Health Insurance Portability and Accountability Act (HIPAA) (United States Department of Health and Human Services; Office for Civil Rights 2017b) permit clinicians to disclose necessary information about a patient to family members, caregivers, law enforcement, or other persons involved with the patient. HIPAA also permits health care providers to disclose necessary information to the patient’s family, friends, or other persons involved in the patient’s care or payment for care when such disclosure is judged to be in the best interests of the patient and the patient is not present or is unable to agree or object to a disclosure due to incapacity or emergency circumstances. Examples of such circumstances are not limited to unconsciousness but may also include circumstances such as temporary psychosis or intoxication with alcohol or other substances (United States Department of Health and Human Services; Office for Civil Rights 2017b).

Although it is beyond the scope of this guideline to discuss the differential diagnosis of psychotic disorders and their evaluation, the clinician should be alert to features of the history that may suggest specific conditions or a need for additional physical or laboratory evaluation. Examples of such conditions that can mimic schizophrenia in their initial presentation include neurosyphilis, velocardiofacial syndrome, Huntington’s disease, Wilson's disease, or anti-NMDA receptor encephalitis
Psychotic symptoms can also occur in the context of other neurological and systemic illnesses, with or without delirium, and such acute states can at times be mistaken for an acute exacerbation of schizophrenia. Furthermore, as new information becomes available about the patient’s illness course and symptoms, the diagnosis may need to be reevaluated because a significant fraction of individuals with psychosis will have a shift in diagnosis over time (Bromet et al. 2011).

Table 1. Recommended aspects of the initial psychiatric evaluation adapted from APA’s Practice Guidelines for the Psychiatric Evaluation of Adults, 3rd edition

History of Present Illness

- Reason that the patient is presenting for evaluation, including current symptoms, behaviors and precipitating factors
- Current psychiatric diagnoses and psychiatric review of systems

Psychiatric History

- Hospitalization and emergency department visits for psychiatric issues, including substance use disorders
- Psychiatric treatments (type, duration, and, where applicable, doses)
- Response and adherence to psychiatric treatments, including psychosocial treatments, pharmacotherapy and other interventions such as electroconvulsive therapy or transcranial magnetic stimulation
- Prior psychiatric diagnoses and symptoms including:
  - Psychotic ideas
  - Aggressive ideas or behaviors (e.g., homicide, domestic or workplace violence, other physically or sexually aggressive threats or acts)
  - Impulsivity
  - Suicidal ideas, suicide plans, and suicide attempts, including details of each attempt (e.g., context, method, damage, potential lethality, intent) and attempts that were aborted or interrupted
  - Intentional self-injury in which there was no suicide intent

Substance Use History

- Use of tobacco, alcohol, and other substances (e.g., marijuana, cocaine, heroin, hallucinogens) and any misuse of prescribed or over-the-counter medications or supplements
- Current or recent substance use disorder or change in use of alcohol or other substances

Medical History

- Whether or not the patient has an ongoing relationship with a primary care health professional
- Allergies or drug sensitivities
- All medications the patient is currently or recently taking and the side effects of these medications (i.e., both prescribed and nonprescribed medications, herbal and nutritional supplements, and vitamins)
- Past or current medical illnesses and related hospitalizations
- Relevant past or current treatments, including surgeries, other procedures, or complementary and alternative medical treatments
- Sexual and reproductive history
- Cardiopulmonary status
- Past or current neurological or neurocognitive disorders or symptoms
- Past physical trauma, including head injuries
• Past or current endocrinological disease
• Past or current infectious disease, including sexually transmitted diseases, HIV, tuberculosis, hepatitis C, and locally endemic infectious diseases such as Lyme disease
• Past or current sleep abnormalities, including sleep apnea
• Past or current symptoms or conditions associated with significant pain and discomfort
• Additional review of systems, as indicated

Family History
• Including history of suicidal behaviors or aggressive behaviors in biological relatives

Personal and Social History
• Preferred language and need for an interpreter
• Personal/cultural beliefs, sociocultural environment and cultural explanations of psychiatric illness
• Presence of psychosocial stressors (e.g., financial, housing, legal, school/occupational, or interpersonal/relationship problems; lack of social support; painful, disfiguring, or terminal medical illness)
• Exposure to physical, sexual, or emotional trauma
• Exposure to violence or aggressive behavior, including combat exposure or childhood abuse
• Legal or disciplinary consequences of past aggressive behaviors

Examination, Including Mental Status Examination
• General appearance and nutritional status
• Height, weight, and body mass index (BMI)
• Vital signs
• Skin, including any stigmata of trauma, self-injury, or drug use
• Coordination and gait
• Involuntary movements or abnormalities of motor tone
• Sight and hearing
• Speech, including fluency and articulation
• Mood, degree of hopelessness, and level of anxiety
• Thought content, process, and perceptions, including current psychotic ideas
• Cognition
• Current suicidal ideas, suicide plans, and suicide intent, including active or passive thoughts of suicide or death
  o If current suicidal ideas are present, assess: patient’s intended course of action if current symptoms worsen; access to suicide methods including firearms; patient’s possible motivations for suicide (e.g., attention or reaction from others, revenge, shame, humiliation, delusional guilt, command hallucinations); reasons for living (e.g., sense of responsibility to children or others, religious beliefs); and quality and strength of the therapeutic alliance.
• Current aggressive ideas, including thoughts of physical or sexual aggression or homicide
  o If current aggressive ideas are present, assess: specific individuals or groups toward whom homicidal or aggressive ideas or behaviors have been directed in the past or at present; impulsivity, including anger management issues and access to firearms
A careful history is also important to identify the presence of co-occurring psychiatric conditions or physical disorders that need to be addressed in treatment planning. For example, the use of cannabis may be more frequent in individuals with schizophrenia (Koskinen et al. 2010) and associated with greater symptom severity or earlier onset of psychosis (Carney et al. 2017; Large et al. 2011). Other substance use disorders, if present, can also produce or exacerbate symptoms of psychosis (American Psychiatric Association 2016; Large et al. 2014).

Mortality is increased in individuals with schizophrenia (Brown et al. 2000; Fazel et al. 2014; Olfson et al. 2015) and the average lifespan is shortened by a decade or more, with much of this decrease related to increased rates of co-occurring physical conditions (Laursen et al. 2013; Saha et al. 2007; Walker et al. 2015). Individuals with serious mental illness have higher rates of smoking, higher rates of heavy smoking, and lower rates of smoking cessation than community samples (Cook et al. 2014; de Leon and Diaz 2005; Myles et al. 2012; Wium-Andersen et al. 2015), each of which contributes to an increased risk of mortality. Many other conditions are more frequent in individuals with serious mental illness in general (Janssen et al. 2015; McGinty et al. 2016) and schizophrenia in particular (Henderson et al. 2015) including, but not limited to: poor oral health (Kisely et al. 2015); hepatitis C infection (Chasser et al. 2017; Hauser and Kern 2015; Hughes et al. 2016); human immunodeficiency virus (HIV) infection (Hobkirk et al. 2015; Hughes et al. 2016); sleep apnea (Myles et al. 2016; Stubbs et al. 2016b); obesity (Janssen et al. 2015); diabetes mellitus (Vancampfort et al. 2016a); metabolic syndrome (Vancampfort et al. 2015); and cardiovascular disease (Correll et al. 2017c). These disorders, if present, can contribute to mortality or reduced quality of life and may be induced or exacerbated by psychiatric medications.

Laboratory tests and physical examination as part of the initial evaluation can help to identify common co-occurring conditions and can serve as a baseline for subsequent monitoring during treatment. (See Table 2).
### Table 2. Suggested physical and laboratory assessments for patients with schizophrenia

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Initial or Baseline</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
<td>Pulse, blood pressure</td>
<td>Pulse; blood pressure; temperature as clinically indicated</td>
</tr>
<tr>
<td>Body weight and height</td>
<td>Body weight, height, and body mass index (BMI)</td>
<td>BMI every visit for 6 months and at least quarterly thereafter</td>
</tr>
<tr>
<td>Hematology</td>
<td>Complete blood count (CBC), including absolute neutrophil count (ANC)</td>
<td>CBC, including ANC if clinically indicated (e.g., patients treated with clozapine)</td>
</tr>
<tr>
<td>Blood chemistries</td>
<td>Electrolytes, Renal function tests, Liver function tests, TSH</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnancy test for women of childbearing potential</td>
<td></td>
</tr>
<tr>
<td>Toxicology</td>
<td>Drug toxicology screen, if clinically indicated</td>
<td>Drug toxicology screen, if clinically indicated</td>
</tr>
<tr>
<td>Electroencephalogram (EEG)</td>
<td>EEG, if indicated based on neurological exam or history</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Brain imaging (CT or MRI, with MRI being preferred), if indicated based on neurological exam or history</td>
<td></td>
</tr>
<tr>
<td>Assessment</td>
<td>Initial or Baselinea</td>
<td>Follow-Upb</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Diabetesd</td>
<td>Screening for diabetes risk factors; fasting blood glucosef</td>
<td>Fasting blood glucose or hemoglobin A1c at 4 months after initiating a new treatment and at least annually thereafterf</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Lipid panelg</td>
<td>Lipid panel at 4 months after initiating a new antipsychotic medication and at least annually thereafter</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>Electrocardiography (ECG) before treatment with chlorpromazine, haloperidol, droperidol, thioridazine, or pimozideh or in the presence of cardiac risk factorsi</td>
<td>ECG with significant change in dose of chlorpromazine, haloperidol, droperidol, thioridazine, or pimozideh or with the addition of other medications that can affect QTc interval in patients with cardiac risk factors or elevated baseline QTc intervalsi</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Screening for symptoms of hyperprolactinemiaj</td>
<td>Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactinj</td>
</tr>
<tr>
<td>Akathisia, dystonia, and parkinsonism</td>
<td>Clinical assessment of akathisia, dystonia, and parkinsonism</td>
<td>Clinical assessment of akathisia, dystonia, and parkinsonism at each visit</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Clinical assessment of abnormal involuntary movements</td>
<td>Clinical assessment of abnormal involuntary movementsl every 6 months in patients at increased risk of tardive dyskinesial and every 12 months in other patientsm</td>
</tr>
</tbody>
</table>
APA’s Practice Guidelines for the Psychiatric Evaluation of Adults, 3rd edition (American Psychiatric Association 2016) recommends that the initial psychiatric evaluation of a patient include assessment of whether or not the patient has an ongoing relationship with a primary care health professional. Preventive care and other tests, such as screening for hepatitis C or HIV, are expected to occur as a part of routine primary care. Nevertheless, determining whether a patient is receiving primary care and inquiring about the patient’s relationship with his or her primary care practitioner can be a starting point for improved access to quality health care and preventive services.

Although this practice guideline recommends that patients treated with antipsychotic medications be monitored for physical conditions and side effects on a regular basis, there are no absolute criteria for frequency of monitoring. Occurrence of conditions and side effects may be influenced by the patient’s history, preexisting conditions, and use of other medications in addition to antipsychotic agents. Thus, decisions about monitoring patients for physical conditions, specific side effects, or abnormalities in laboratory test results will necessarily depend on the clinical circumstances. In general, assessments related to physical conditions and specific medication-related side effects will be done at the time of initiating or changing antipsychotic medications or when adding other medications that contribute to these side effects.

BMI may be calculated by using the formula weight in kg/(height in m)² or the formula 703 × weight in lb/(height in inches)² or by using a BMI calculator available from the National Heart Lung and Blood Institute (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm). A person with a BMI >25 to 29.9 is considered overweight, and one with a BMI of 30 or higher is considered obese. In addition to BMI, waist circumference can be used as an indicator of risk (>35 inches for women and >40 inches for men). Except for patients with a BMI of <18.5, an increase in BMI of 1 BMI unit would suggest a need for intervention by monitoring weight more closely, engaging the patient in a weight management program, using an adjunctive treatment to reduce weight, or changing the antipsychotic medication.

The U.S. Food and Drug Administration has requested all manufacturers of second-generation antipsychotic medications (SGAs) to include a warning in their product labeling regarding hyperglycemia and diabetes mellitus. Although precise risk estimates for hyperglycemia-related adverse events are not available for each agent, epidemiological studies suggested an increased risk of treatment-emergent adverse events with SGAs. In some patients, this hyperglycemia was extreme and/or associated with ketoacidosis, hyperosmolar coma, or death.

Factors that indicate an increased risk for undiagnosed diabetes include a BMI greater than 25, a first-degree relative with diabetes, habitual physical inactivity, being a member of a high-risk ethnic population (African American, Hispanic American, Native American, Asian American, Pacific Islander), history of cardiovascular disease, hypertension (≥140/90 mmHg or on therapy for hypertension), HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L), polycystic ovary syndrome (in women), having had gestational diabetes, and other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans) (American Diabetes
Symptoms of possible diabetes include frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurry vision.

When screening for the presence of diabetes, criteria for diagnosis (American Diabetes Association 2018) include a fasting plasma glucose higher than 125 mg/dL, where fasting is defined as no caloric intake for at least 8 hours. Alternatively, a hemoglobin A1C of 6.5% or greater can be used. Other acceptable approaches for diagnosis of diabetes include an oral glucose tolerance test or a random plasma glucose of at least 200 mg/dL in conjunction with a hyperglycemia crisis or classic symptoms of hyperglycemia. With all of these approaches, results should be confirmed by repeat testing unless unequivocal hyperglycemia is present. In patients with hemoglobinopathies or conditions associated with increased red blood cell turnover (e.g., second or third trimester pregnancy, hemodialysis, recent blood loss, transfusion, erythropoietin therapy), fasting plasma glucose should be used rather than hemoglobin A1C. An abnormal value of fasting plasma glucose or hemoglobin A1C suggests a need for medical consultation. More frequent monitoring may be indicated in the presence of weight change, symptoms of diabetes, or a random measure of blood glucose >200 mg/dl.

Additional information on screening and management of patients with lipid disorders can be found in the AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (Grundy et al. 2018).

Using an Adverse Drug Event Causality Analysis intended to evaluate the risk of sudden death when taking a specific medication (Woosley et al. 2017), the listed drugs have been categorized as prolonging the QT interval and being clearly associated with a known risk of torsades de pointes (TdP), even when taken as recommended (Woosley et al. 2019).

In this context, cardiac risk factors include factors associated with inherited long QT syndromes (Funk et al. 2018) (such as family history of an early age of sudden death, near drowning, or drowning; personal history of near drowning, unexplained seizures or unexplained syncope; and congenital deafness, which can be due to the same underlying genetic cause as inherited long QT syndrome) and factors associated with an increased risk of acquired long QT prolongation or TdP (including structural or functional heart disease; starvation; bradycardia; risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia; excess dose or rapid intravenous infusion of QTc interval prolonging drugs; simultaneous use of multiple drugs that prolong QTc intervals; or factors affecting drug metabolism such as metabolizer status, drug-drug interactions, acute or chronic kidney disease, or hepatic impairment). Women and older individuals also have an increased risk of TdP.

Changes in libido, menstrual changes, or galactorrhea in women; changes in libido or in erectile or ejaculatory function in men.

Assessment can occur through clinical examination or through the use of a structured evaluative tool such as the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976; Munetz and Benjamin 1988). (For a copy of the AIMS scale, see: http://cqaimh.org/pdf/tool_aims.pdf.)
Patients at increased risk for developing abnormal involuntary movements include individuals older than 55 years; women; individuals with a mood disorder, intellectual disability, or central nervous system injury; and patients who experience acute dystonic reactions, clinically significant parkinsonism, or akathisia (Solmi et al. 2018b). Abnormal involuntary movements can also emerge or worsen with antipsychotic cessation.

Frequency of monitoring for involuntary movements in individuals receiving treatment with an antipsychotic medication is also subject to local regulations in some jurisdictions.
As part of the initial evaluation, it is also useful to inquire about the course and duration of symptoms prior to treatment (i.e., duration of untreated psychosis) (Penttilä et al. 2014; Register-Brown and Hong 2014; Santesteban-Echarri et al. 2017) and whether the patient has received any mental health treatment. If so, it is important to ask about a broad range of treatments and other approaches to addressing the patient’s symptoms and functioning and to specifically ask about the full range of treatment settings (e.g., outpatient, partial hospitalization, inpatient) and approaches that the patient has found helpful or problematic (American Psychiatric Association 2016). Although most patients will comment on prior medications, psychotherapy, or psychiatric hospitalizations if asked about treatment history, specific questions may be needed to gather details of such treatments. Prompting may be needed to learn information about the patient’s experiences with other interventions such as psychosocial rehabilitation, supported employment, assertive community treatment, court-ordered treatment, treatment while incarcerated, substance use treatments, neuromodulatory therapies (e.g., electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS)), 12-step programs, self-help groups, spiritual healers, and complementary or alternative treatment approaches. Pharmacy databases and patients’ lists of active medications are not likely to include long-acting injectable (LAI) medications (e.g., antipsychotics, naltrexone) or implants (e.g., buprenorphine, contraceptive agents), over-the-counter medications, herbal products, or nutritional supplements. For each specific type of intervention that the patient has received, it is helpful to learn more about the duration, mode of delivery (e.g., formulation, route, and dose for medications; format, type, and frequency of treatment for psychotherapy), response (including tolerability, changes in quality of life, level of functioning, and symptom response/remission), and degree of adherence.

Risk assessment is another essential part of the initial psychiatric evaluation (American Psychiatric Association 2004) as modifiable risk factors for suicidal or aggressive behaviors identified during the assessment can serve as targets of intervention in constructing a plan of treatment. Suicidal ideas are common in individuals with schizophrenia, and death due to suicide has been estimated to occur in about 4%-10% of individuals (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; Tanskanen et al. 2018; Yates et al. 2019), yielding a greater than 10-fold increase in standardized mortality ratios (Saha et al. 2007). Among individuals with schizophrenia, suicide attempts and suicide may be more common early in the course of the illness (Popovic et al. 2014) and can even occur before initial treatment for psychosis (Challis et al. 2013).

In individuals with schizophrenia, many of the risk factors that contribute to the risks of suicidal or aggressive behaviors are the same as factors increasing risk in other disorders. For example, in individuals with schizophrenia, an increased risk of suicidal or aggressive behaviors has been associated with male sex, expressed suicidal ideation, a history of attempted suicide or other suicide-related behaviors, and the presence of alcohol use disorder or other substance use disorder (Cassidy et al. 2018; Challis et al. 2013; Fazel et al. 2009a; Fazel et al. 2014; Fleischhacker et al. 2014; Hawton et al. 2005; Hor and Taylor 2010; Østergaard et al. 2017; Pompili et al. 2007; Popovic et al. 2014; Roché et al. 2018; Sariaslan et al. 2016; Singh et al. 2012; Swanson et al. 2006; Witt et al. 2013; Witt et al. 2014). Firearm access is an additional contributor to suicide risk (Alban et al. 2018; Anestis et al. 2018; Siegel and...
Rothman 2016). Additional risk factors for suicide among individuals with schizophrenia include depressive symptoms, hopelessness, recency of diagnosis or hospitalization, repeated hospitalizations, high intelligence, young age, and poor adherence to treatment (Cassidy et al. 2018; Fleischhacker et al. 2014; Popovic et al. 2014; Randall et al. 2014). Other factors that have been identified as increasing risk among individuals with schizophrenia include agitation or motor restlessness, fear of mental disintegration, recent loss, and poor adherence to treatment (Hawton et al. 2005; Lopez-Morinigo et al. 2014; Pompili et al. 2007). It is not clear whether preserved insight is associated with an increase in suicide risk among individuals with schizophrenia (Hor and Taylor 2010) or whether this is an apparent increase that is mediated by other factors such as hopelessness (López-Morinigo et al. 2012). Although reduced risk of suicide was associated with hallucinations in one meta-analysis (Hawton et al. 2005), the presence of auditory command hallucinations may confer increased risk (Harkavy-Friedman et al. 2003; Wong et al. 2013). Command hallucinations can also be relevant when assessing individuals for a risk of aggressive behaviors (McNiels et al. 2000; Swanson et al. 2006) although the relationship between experiencing commands and acting on them is complex (Braham et al. 2004). Persecutory delusions may also contribute to risk of aggression, particularly in the absence of treatment or in association with significant anger (Coid et al. 2013; Keers et al. 2014; Swanson et al. 2006). Among individuals with psychotic illnesses, prior suicidal threats, angry affect, impulsivity, hostility, recent violent victimization, childhood sexual abuse, medication nonadherence, and a history of involuntary treatment were also associated with an increased risk of aggressive behavior (Buchanan et al. 2019; Large and Nielssen 2011; Reagu et al. 2013; Swanson et al. 2006; Witt et al. 2013; Witt et al. 2014). Other factors associated with a risk of aggression are similar to findings in individuals without psychosis and include male sex, young age, access to firearms, the presence of substance use, traumatic brain injury, a history of attempted suicide or other suicide-related behaviors, or prior aggressive behavior, including that associated with legal consequences (Buchanan et al. 2019; Cassidy et al. 2018; Fazel et al. 2009a, 2009b; Fazel et al. 2014; Fleischhacker et al. 2014; Large and Nielssen 2011; Monuteaux et al. 2015; Østergaard et al. 2017; Popovic et al. 2014; Roché et al. 2018; Sariaslan et al. 2016; Short et al. 2013; Singh et al. 2012; Swanson et al. 2006; Witt et al. 2013; Witt et al. 2015).

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

In an individual with a possible psychotic disorder, a detailed assessment is important in establishing a diagnosis, recognizing co-occurring conditions (including substance use disorders, other psychiatric disorders, and other physical health disorders), identifying psychosocial issues, and developing a plan of treatment that can reduce associated symptoms, morbidity, and mortality.

**Harms**

Some individuals may become anxious, suspicious, or annoyed if asked multiple questions during the evaluation. This could interfere with the therapeutic relationship between the patient and the clinician.

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* Harms may include serious adverse events, less serious adverse events that affect tolerability, minor adverse events, negative effects of the intervention on quality of life, barriers and inconveniences associated with treatment and other negative aspects of the treatment that may influence decision making by the patient, the clinician or both.
Another potential consequence is that time used to focus on a detailed assessment (as outlined in the *Practice Guidelines for the Psychiatric Evaluation of Adults*) could reduce time available to address other issues of importance to the patient or of relevance to diagnosis and treatment planning.

**Patient Preferences**

Although there is no specific evidence on patient preferences related to assessment in individuals with a possible psychotic disorder, clinical experience suggests that the majority of patients are cooperative with and accepting of these types of questions as part of an initial assessment.

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. This recommendation is also consistent with the APA *Practice Guidelines for the Psychiatric Evaluation of Adults* (American Psychiatric Association 2016). The level of research evidence is rated as low because there is minimal research on the benefits and harms of assessing these aspects of history and examination as part of an initial assessment. Nevertheless, expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves the diagnosis and treatment planning in individuals with a psychiatric disorder (for additional details, see American Psychiatric Association 2016). (For additional discussion of the research evidence, see Appendix C, Statement 1.)

**Differences of Opinion Among Writing Group Members**

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

**Review of Available Guidelines from Other Organizations**

Relevant guidelines from the following organizations were reviewed: British Association for Psychopharmacology (BAP), Canadian Schizophrenia Guidelines (CSG), National Institute for Health and Care Excellence (NICE), Royal Australian and New Zealand College of Psychiatry (RANZCP), Scottish Intercollegiate Guidelines Network (SIGN), World Federation of Societies of Biological Psychiatry (WFSBP), and Schizophrenia Patient Outcomes Research Team (PORT). Information from them is generally consistent with this guideline statement. Other guidelines on the treatment of schizophrenia incorporate recommendations related to the need for a comprehensive initial assessment (Addington et al. 2017a; National Institute for Health and Care Excellence 2014) including identification of prior and current psychiatric symptoms and diagnoses (Addington et al. 2017a; Hasan et al. 2015; National Institute for Health and Care Excellence 2014), assessment of substance use (Addington et al. 2017a; Barnes et al. 2011; Crockford and Addington 2017; Galletly et al. 2016; National Institute for Health and Care Excellence 2014), physical health history and examination (Addington et al. 2017a; National Institute for Health and Care Excellence 2014), assessment of psychosocial factors (Addington et al. 2017a; Galletly et al. 2016; National Institute for Health and Care Excellence 2014), and assessment of the risk of harm to self or others (Addington et al. 2017a; Hasan et al. 2015; National Institute for Health and Care Excellence 2014). Several other guidelines also provide information on the circumstances in which an electrocardiogram is suggested (Barnes et al. 2011; National Institute for Health and Care Excellence 2014; Pringsheim et al. 2017).
Quality Measurement Considerations

For patients with psychotic disorders, including schizophrenia, several components of the initial psychiatric evaluation have potential relevance for quality measure development, although such quality measures do not exist at present. Furthermore, to develop quality measures that are scientifically sound, indicators that signal the delivery of high-quality care during the evaluation must first be defined. Given the breadth of content within the initial psychiatric evaluation, it may be difficult to identify a discrete process that could be readily ascertained from chart or administrative data. However, it may still be possible to develop and specify electronic and clinical data registry quality measures based on available evidence and expert-recommended consensus. Additionally, as discussed in the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association 2016), quality improvement efforts at the local level could assess whether specific aspects of the evaluation such as a risk assessment were completed while still allowing flexibility in the documentation of findings.

Statement 2

APA recommends (1C) that the initial psychiatric evaluation of a patient with a possible psychotic disorder include a quantitative measure to identify symptoms that may be the focus of treatment and to determine their severity.*

Implementation

APA’s Practice Guidelines for the Psychiatric Evaluation of Adults, 3rd edition (American Psychiatric Association 2016) provides a general description of the use of quantitative measures as part of the initial psychiatric evaluation. In the assessment of a patient with a possible psychotic disorder, quantitative measures can also be used to help detect and determine the severity of psychosis and associated symptoms. The intent of using a quantitative measure is not to establish a diagnosis but rather to complement other aspects of the screening and assessment process. Depending on the measure, it can aid in treatment planning by providing a structured replicable way to document the patient’s baseline symptoms. It can also help to determine which symptoms should be the target of intervention based on factors such as frequency of occurrence, magnitude, potential for associated harm to the patient or others, and associated distress to the patient.

As treatment proceeds, use of quantitative measures allows more precise tracking of whether nonpharmacological and pharmacological treatments are having their intended effect or whether a shift in the treatment plan is needed. This record of a patient’s response to treatment is of particular value when the treatment is nonstandard (e.g., combination of antipsychotics) or expensive. It can also provide helpful information about the actual effects of prior treatments. In addition, patients’ ratings can be compared with family members’ impressions of treatment effects to clarify the longitudinal course of the patient’s illness.

Much of the treatment-related research in psychiatry has used clinician-rated scales to determine patient outcomes; however, patient-rated scales are typically less time-consuming to administer than

* 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.
clinician-rated scales. In addition, they provide important insights into the patient’s experience that support person-centered care. The use of anchored, self-rated scales with criteria to assess the severity and frequency of symptoms can also help patients become more informed self-observers. However, correlations between patient- and clinician-rated scales are often modest (Harvey 2011; Spitz et al. 2017), suggesting that both types of quantitative measures provide useful information.

The exact frequency at which measures are warranted will depend on clinical circumstances. Use of quantitative measures over time will help assure that key elements of information are collected to guide treatment. Consequently, it is preferable to use a consistent approach to quantitative measurement for a given patient as each rating scale defines and measures psychosis and other symptoms differently.

Although recommending a particular scale, patient- or clinician-rated, is outside the scope of this practice guideline, a number of objective, quantitative rating scales to monitor clinical status in schizophrenia are available (American Psychiatric Association 2013a; Rush et al. 2008). The Clinician-Rated Dimensions of Psychosis Symptom Severity (American Psychiatric Association 2013b), which is included in DSM-5 for further research and clinical evaluation, contains 8 domains that are rated on a scale from 0 (not present) to 4 (present and severe) based on symptoms in the prior 7 days. A 6-item version of the Positive and Negative Syndrome Scale (PANSS-6) (Østergaard et al. 2018b; Bech et al. 2018) consists of the PANSS items for delusions, conceptual disorganization, hallucinations, blunted affect, social withdrawal, and lack of spontaneity and flow of conversation (Kay et al. 1987). Data on the PANSS-6 suggests that it correlates highly with scores on the 30-item version of the Positive and Negative Syndrome Scale (PANSS-30) (Østergaard et al. 2018a, 2018b). Furthermore, it is sensitive to changes with treatment and able to identify symptom remission with a high degree of accuracy (Østergaard et al. 2018a, 2018b) if individuals who are performing ratings are appropriately trained (Opler et al. 2017). Clinician-rated scales may also be selected to assess specific clinical presentations, such as using the Bush-Francis Catatonia Rating Scale for individuals with catatonic features (Bush et al: 1996a). Other clinician-rated scales are commonly used for monitoring psychopathology in research but are likely to be too lengthy for routine clinical use. These include the PANSS-30 (Kay et al. 1987), the Assessment of Negative Symptoms (SANS; Andreasen 1984a), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b) and the Brief Psychiatric Rating Scale (BPRS; Leucht et al. 2005; Overall and Gorham 1962; Ventura et al. 1993a, 1993b).

In terms of patient-rated scales, the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure, Adult (American Psychiatric Association 2013c) includes a total of 23 items in 13 domains with only 2 items related to psychosis. Nevertheless, it may be useful for identifying and tracking symptoms other than psychosis, including those related to co-occurring disorders. DSM-5 also includes 36-item, self- and proxy-administered versions of the World Health Organization Disability Schedule 2.0 (WHODAS 2.0) for assessing functioning difficulties due to health and mental health conditions (American Psychiatric Association 2013d; Üstün et al. 2010). Other options for assessing functioning include the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association 2000) and the Personal and Social Performance scale (Morosini et al. 2000). The use of ratings from other informants is particularly helpful in assessing the patient’s level of functioning because individuals with schizophrenia
often have a different view of their functioning than family members or others involved in their lives (Harvey 2011).

To assess overall satisfaction with mental health, a single-item can be used in which the question "How satisfied are you with your mental health?" is rated on a 7-point scale ranging from "couldn't be worse" to "couldn't be better" (McGranahan et al. 2018). In addition to the rapidity of administration, ratings on this single item appear to be associated with symptom severity on PANSS and BPRS domains, particularly those related to affective and negative symptoms (McGranahan et al. 2018). For a nonspecific measure of quality of life, patients can be asked to rate their overall (physical and mental) quality of life in the past month on a scale from 0 (“about as bad as dying”) to 10 (“life is perfect”) (Unützer et al. 2002). In individuals with chronic mental illness, the Satisfaction With Life Scale (Diener et al. 1985) has been developed and used to assess life satisfaction and quality of life. Quality of life can also be measured using a scale developed by the World Health Organization, the WHOQOL-BREF (Skevington et al. 2004; The WHOQOL Group 1998) (http://depts.washington.edu/seagol/WHOQOL-BREF). The Centers for Disease Control and Prevention Healthy Days Measure (HRQOL-14) and core module (HRQOL-4) (http://www.cdc.gov/hrqol/hrqol14_measure.htm) have also been used in general population samples to assess physical and emotional symptoms as related to an individual’s perceived sense of well-being (Moriarty et al. 2003).

Rating scales should always be implemented in a way that supports developing and maintaining the therapeutic relationship with the patient. If more than one quantitative measure is being used, it is important to minimize duplication of questions and avoid overwhelming the patient with an excessive number of scales to complete. In addition, when choosing among available quantitative measures, objectives of scale use (e.g., screening, documenting baseline symptoms, ongoing monitoring) should be considered. Optimal scale properties (e.g., sensitivity, specificity) will differ depending on the desired purpose, yet assessments of scale validity and reliability are typically conducted cross-sectionally in research contexts.

Because many scales ask the patient to rate symptoms over several weeks, they may not be sensitive to change. This can be problematic in acute care settings, where treatment adjustments and symptom improvement can occur fairly quickly. Some symptom-based quantitative measures focus either on symptom frequency over the observation period or on symptom severity. Although these features often increase or decrease in parallel, that is not invariably the case. Other quantitative measures ask the patient to consider both symptom frequency and severity, which can also make the findings difficult to interpret.

Other factors that can affect the statistical reliability and validity of rating scale measures include comorbid illnesses and patient age, language, race, ethnicity, cultural background, literacy, and health literacy. These factors and others can lead patients to misinterpret questions or bias the ratings that they record, either unintentionally (e.g., to please the clinician with their progress) or intentionally (e.g., to obtain controlled substances, to support claims of disability). Thus, the answers to questions and the summative scores on quantitative measures need to be interpreted in the context of the clinical presentation.
The type and extent of quantitative measures used will also be mediated by the clinical setting, the time that is available for evaluation, and the urgency of the situation. In some clinical contexts, such as a planned outpatient assessment, patients may be asked to complete electronic- or paper-based quantitative measures, either prior to the visit or upon arrival at the office (Allen et al. 2009; Harding et al. 2011). Between or prior to visits, electronic approaches (e.g., mobile phone applications, clinical registries, patient portal sites in electronic health records) may also facilitate obtaining quantitative measurements (Palmier-Claus et al. 2012; Wang et al. 2018a). In other clinical contexts, such as acute inpatient settings, electronic modes of data capture may be more cumbersome, and patients may need more assistance in completion of scales. As an alternative, printed versions of scales may be completed by the patient or a proxy or administered by the clinician. In other clinical circumstances, however, printed or electronic versions of quantitative scales may not be readily available or information may not be available to complete all scale items. In emergency settings, use of a quantitative rating scale may need to be postponed until the acute crisis has subsided or until the patient’s clinical status permits a detailed examination including use of quantitative rating scales.

Although available information suggests that ambulatory patients are generally cooperative, some individuals may be unwilling to complete quantitative measures (Narrow et al. 2013). Severe symptoms, co-occurring psychiatric conditions, low health literacy, reading difficulties, or cognitive impairment may limit some patients’ ability to complete self-report instruments (Harding et al. 2011; Valenstein et al. 2009; Zimmerman et al. 2011). In these circumstances, it may be necessary to place greater reliance on collateral sources of information such as family members, other treating health professionals, or staff members of community residence programs, if applicable. If collateral sources of information are not immediately available, treatment may also need to proceed, with adjustments in the plan, if indicated, as additional knowledge is gained. If time constraints are present, the clinician may wish to focus on rating of relevant target symptoms (e.g., on a Likert scale). In emergent circumstances, safety of the patient and others must take precedence; the initial assessment may need to be brief, with a more detailed assessment and incorporation of quantitative measures once the acute clinical situation has been stabilized.

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Clinical decision making, including but not limited to diagnosis and treatment planning, requires a careful and systematic assessment of the type, frequency, and magnitude of psychiatric symptoms as well as an assessment of the impact of those symptoms on the patient’s day-to-day functioning and quality of life. Intuitively, and by analogy with other medical specialties in which treatment is guided by standardized measurement (e.g., of physiological signs or laboratory tests), the use of a systematic and quantifiable approach to assessment would seemingly produce better patient outcomes and greater standardization of care across patients. As electronic health records become more commonly used, electronic capture of quantitative measures can facilitate use of computerized decision-support systems in guiding evidence-based treatment, catalyzing additional improvements in outcomes and quality of care.
Use of a quantitative measure as part of the initial evaluation can establish baseline information on the patient’s symptoms and level of functioning and can help determine specific targets of treatment in the context of shared decision-making. When administered through paper-based or electronic self-report and as compared with a clinical interview, use of a quantitative measure may help the clinician to conduct a more consistent and comprehensive review of the multiplicity of symptoms that the patient may be experiencing. Using systematic measures may also increase the efficiency of asking routine questions and allow more time for clinicians to focus on symptoms of greatest severity or issues of most concern to the patient. Such measures may also facilitate collection of information from the patient’s family or other collateral informants on factors such as symptoms or functioning. When used on a longitudinal basis, quantitative measures can help determine whether nonpharmacological and pharmacological treatments are having their intended effect or whether a shift in the treatment plan is needed to address symptoms, treatment-related side effects, level of distress, functioning impairments, or potential for harm to the patient or others. Without the use of a consistent quantitative measure, recall biases may confound the ability of patients and clinicians to compare past and current levels or patterns of symptoms and functioning. When patients have had substantial improvements in symptoms and functioning, it can be easy to focus on the improvements and overlook residual symptoms or side effects of treatment that are contributing to ongoing impairment or quality of life. Thus, ongoing use of quantitative assessments may foster identification of residual symptoms or impairments and early detection of illness recurrence. Systematic use of quantitative measures can also facilitate communication among treating clinicians and can serve as a basis for enhanced management of populations of patients as well as individual patients.

Harms

The harms of using a quantitative measure include the time required for administration and review. The amount of time available for an initial psychiatric evaluation is typically constrained by clinician availability, cost, and other factors. Under such circumstances, time that is used to obtain quantitative measures could introduce harms by reducing time available to address other issues of importance to the patient or of relevance to clinical decision making. Overreliance on quantitative measures may also cause other aspects of the patient’s symptoms and clinical presentation to be overlooked. Some patients may view quantitative measures as impersonal or may feel annoyed by having to complete detailed scales, particularly if done frequently. If a patient feels negatively about quantitative measures, this could alter the therapeutic alliance. In addition, some patients may have difficulty completing self-report scales or may interpret questions incorrectly. Patients may also provide inaccurate information about their symptoms and relying on inaccurate information can have a negative impact on clinical decision-making, including recommendations for treatment. Systematic use of measures may require changes in workflow or staffing to distribute scales, increase time needed to review results with the patient or lead to unreimbursed costs (e.g., to integrate measures into electronic health record systems, to pay to use copyrighted versions of scales).
Patient Preferences

Clinical experience suggests that the majority of patients are cooperative with and accepting of quantitative measures as part of an initial or subsequent assessment. Most patients will be able to appreciate the ways in which the use of quantitative measures will be of benefit to them. For example, in the testing of the DSM-5 Cross Cutting Symptom Measure as part of the DSM-5 field trials, quantitative measures were found to be acceptable to patients (Clarke et al. 2014; Mościcki et al. 2013) and only a small fraction of individuals felt that measurement of symptoms would not be helpful to their treating clinician (Mościcki et al. 2013).

The fact that the clinician is using a systematic approach to address the patients’ symptoms and functioning sends a positive message that could improve the therapeutic relationship. Especially in developed countries, patients are used to and expect digital, computerized information exchange, including for health-related monitoring and communication. For these patients, the use of quantitative measures within the context of an electronic health record, mobile app, or other computerized technology may be more convenient and have positive effects on the relationship of the patient with the clinician and the health system.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. This recommendation is also consistent with Guideline VII, “Quantitative Assessment,” as part of the APA’s Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association 2016). Although quantitative measures have been used for reporting purposes as well as research, the level of research evidence for this recommendation is rated as low because it remains unclear whether routine use of these scales in clinical practice improves overall outcomes. Nonetheless, expert opinion suggests that use of quantitative measures will enhance clinical decision making and improve treatment outcomes. (For additional discussion of the research evidence, see Appendix C, Statement 2.)

There is minimal research on the harms of using quantitative measures as part of the psychiatric evaluation as compared with assessment as usual. However, expert opinion suggests that harms of assessment are minimal compared with the benefits of such assessments in improving identification and assessment of psychiatric symptoms. (For additional details, see the APA’s Practice Guidelines for the Psychiatric Evaluation of Adults; American Psychiatric Association 2016).

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Multiple guidelines from other organizations were reviewed (Addington et al. 2017a, 2017b; Barnes et al. 2011; Buchanan et al. 2010; Crockford and Addington 2017; Hasan et al. 2012; Hasan et al. 2013; Hasan et al. 2015; Galletly et al. 2016; National Institute for Health and Care Excellence 2014; Norman et al. 2017; Pringsheim et al. 2017; Scottish Intercollegiate Guidelines Network 2013). None of these guidelines specifically recommend using quantitative measures as part of the initial assessment in
individuals with schizophrenia but several guidelines (Barnes et al. 2011; Galletly et al. 2016) do recommend use of rating scales under some circumstances at baseline or as part of ongoing monitoring.

**Quality Measurement Considerations**

While evidence suggests that there is insufficient consensus recommending the use of specific patient-reported quantitative measures for use by individuals with psychotic disorders, including schizophrenia, there is data supporting the implementation of provider-reported symptom reduction or maintenance tools for this patient population. As such this recommendation would not be appropriate for use as a highly-specified, stand-alone quality measure. Nevertheless, a process-focused internal or health system-based quality improvement measure could determine rates of quantitative measure use and implement quality improvement initiatives to increase the frequency with which such measures are used in individuals with schizophrenia.

**Statement 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.*

**Implementation**

In treating individuals with schizophrenia, a person-centered treatment plan should be developed, documented in the medical record, and updated at appropriate intervals. A person-centered treatment plan can be recorded as part of an evaluation note or progress note and does not need to adhere to a defined development process (e.g., face-to-face multidisciplinary team meeting) or format (e.g., time-specified goals and objectives). Depending on the urgency of the initial clinical presentation, the availability of laboratory results, and other sources of information, the initial treatment plan may need to be augmented over several visits as more details of history and treatment response are obtained.

As treatment proceeds, the treatment plan will require iterative re-evaluation and adjustment prompted by factors such as inadequate treatment response, difficulties with tolerability or adherence, changes in presenting issues or symptoms, or revisions in diagnosis. For most individuals with schizophrenia, it is challenging to piece together a coherent picture of the patient's longitudinal course from medical records. It is important to note the rationale for any changes in the treatment plan as well as the specific changes that are being made because an accurate history of past and current treatments and responses to them is a key part of future treatment planning.

The overarching aims of treatment planning are severalfold: 1) to promote and maintain recovery, 2) to maximize quality of life and adaptive functioning, and 3) to reduce or eliminate symptoms. To achieve these aims, it is crucial to identify the patient’s aspirations, goals for treatment and treatment-related preferences. For patients who have completed a psychiatric advance directive (Easter et al. 2017; Kemp et al. 2015, Shields et al. 2014; Wilder et al. 2010), wellness recovery action plan (National Alliance on Mental Illness 2018), or individualized crisis prevention or safety plans (Safety Planning Intervention 2018; Stanley and Brown 2012; Stanley et al. 2018), these documents will be important to review with

* 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.
the patient in crafting a person-centered approach to care. Discussion with the patient, other treating health professionals, family members, and others involved in the patient's life can each be vital in developing a full picture of the patient and formulating a person-centered treatment plan. The patient and others may express opinions about specific treatment approaches or identify practical barriers to the patient's ability to participate in treatment, such as cognitive impairments, disorganization, or inadequate social resources. Family members and others involved in the patient's life may also express specific concerns about the individual's symptoms or behaviors, which, if present, should be documented and addressed. Discussions with the patient, family members, and others will typically occur as part of the initial assessment (See Statement 1), but family members can be an important part of the care team and additional input will be needed as treatment proceeds and the treatment plan is updated. Collaboration and communication with other treating health professionals is also essential to avoid fragmentation of treatment efforts.

Depending on the clinical circumstances and input from the patient and others, a comprehensive and person-centered treatment plan will typically delineate treatments aimed at improving functioning, reducing positive and negative symptoms, and addressing co-occurring psychiatric symptoms or disorders. In each of these respects, it is essential to consider both nonpharmacological and pharmacological treatment approaches and recognize that a combination of nonpharmacological and pharmacological treatments will likely be needed to optimize outcomes. Other elements of the treatment plan may include:

- determining the most appropriate treatment setting,
- delineating plans for addressing risks of harm to self or others (if present)
- addressing barriers to adherence
- engaging family members and others involved in the patient's life
- providing information to patients, family members, and others involved in the patient's life about treatment options, early symptoms of relapse, need for ongoing monitoring, coping strategies, case management services, and community resources (such as the National Alliance on Mental Illness)
- incorporating goals of treatment related to:
  - social support networks
  - interpersonal, family, or intimate relationships
  - parenting status
  - living situation
  - past trauma or victimization
  - school or employment
  - financial considerations, including disability income support, when indicated
  - insurance status
  - legal system involvement
- identifying additional needs for:
  - history or mental status examination
  - physical examination (either by the evaluating clinician or another health professional)
• laboratory testing, imaging, electrocardiography, or other clinical studies (if indicated based on the history, examination, and planned treatments)

• collaborating with other treating clinicians (including provision of integrated care) to assure that co-occurring substance use disorders and physical health conditions are managed

In determining a treatment setting, considerations for individuals with schizophrenia are similar to those for individuals with other diagnoses. Thus, in general, patients should be cared for in the least restrictive setting that is likely to be safe and to allow for effective treatment. If inpatient care is deemed essential, efforts should be made to hospitalize patients voluntarily. Indications for hospitalization usually include the patient posing a serious threat of harm to self or others or being unable to care for self and needing constant supervision or support as a result. Other possible indications for hospitalization include general medical or psychiatric problems that make outpatient treatment unsafe or ineffective or new onset of psychosis that warrants initial inpatient stabilization to promote reduction of acute symptoms and permit engagement in treatment. Less restrictive settings may be indicated when a patient does not meet criteria for inpatient treatment but requires more monitoring or assistance than is available in routine outpatient care. Such settings may include assertive community treatment (U.S. Department of Health and Human Services; Substance Abuse and Mental Health Services Administration 2008), intensive outpatient treatment, partial hospitalization, or day hospitalization.

Identifying risk factors and estimating risks for suicidal and aggressive behaviors are essential parts of psychiatric evaluation (American Psychiatric Association 2016 and as described in detail in the Implementation section of Statement 1 of this guideline). Despite identification of these risk factors, it is not possible to predict whether an individual patient will engage in aggressive behaviors or attempt or die by suicide. However, when an increased risk for such behaviors is present, it is important that the treatment plan incorporate approaches that target and aim to reduce modifiable risk factors. Although demographic and historical risk factors are static, a number of these risk factors are potentially modifiable and can be addressed in the treatment plan through a focus on core symptoms of schizophrenia (e.g., hallucinations, delusions), co-occurring symptoms (e.g., depression, hopelessness, hostility, impulsivity), co-occurring diagnoses (e.g., depression, alcohol use disorder, other substance use disorders), or planning to address periods of increased risk (e.g., shortly after diagnosis, subsequent to hospital discharge).

Individuals with schizophrenia have high rates of nicotine dependence (Centers for Disease Control and Prevention 2019; Dickerson et al. 2018; Smith et al. 2014), cannabis use (Brunette et al. 2018; Hunt et al. 2018; Nesvåg et al. 2015; Toftdahl et al. 2016), and use of alcohol and other substances (Brunette et al. 2018; Hunt et al. 2018; Nesvåg et al. 2015; Toftdahl et al. 2016). The adverse health consequences of smoking are well documented (U.S. Department of Health and Human Services 2014; Van Schayck et al. 2017). Although quit rates may be lower in individuals with schizophrenia than in the general population (Lum et al. 2018), smoking cessation is recommended. Some studies have assessed smoking cessation approaches targeted to individuals with mental illnesses, but specific evidence in patients with schizophrenia is still limited (Sharma et al. 2017). Thus, smoking cessation approaches will typically follow guidelines for the general population (National Cancer Institute 2019; SAMHSA-HRSA Center for
Integrated Health Solutions 2018; Siu et al. 2015; Van Schayck et al. 2017; Verbiest et al. 2017). In addition, health education and motivational interviewing approaches can be helpful in those who are ambivalent about stopping cigarette use (Levounis et al. 2017). Cannabis use has been associated with an increased incidence of schizophrenia (Nielsen et al. 2017) and it may also contribute to a higher burden of symptoms (Oluwoye et al. 2018). Other substance use disorders are associated with a poorer prognosis in individuals with schizophrenia (Brunette et al. 2018; Conus et al. 2017; Weibell et al. 2017) and, as noted previously, can contribute to risk of suicide or aggressive behavior. Thus, it is important for the treatment plan to address substance use disorders when they are present. A comprehensive integrated treatment model is often suggested in which the same clinicians or team of clinicians provide treatment for schizophrenia as well as treatment of substance use disorders. However, if an integrated treatment is unavailable, the treatment plan should address both disorders with communication and collaboration among treating clinicians. For patients who do not recognize the need for treatment of a substance use disorder, a stage-wise motivational approach can be pursued (Catley et al. 2016; Levounis et al. 2017).

Depressive symptoms are common in individuals with schizophrenia and should be addressed as part of treatment planning. The approach to treating depression will be grounded in a careful differential diagnosis that considers the possible contributions of demoralization, negative symptoms of schizophrenia, side effects of antipsychotic medications, substance intoxication or withdrawal, physical health condition, or a co-occurring major depressive episode. Depressive symptoms that occur during an acute episode of psychosis often improve as psychotic symptoms respond to treatment. Evidence on the use of antidepressants to treat depression in individuals with schizophrenia comes from multiple trials, many of which have small sample sizes or factors that increase the risk of bias in the findings (Dondé et al. 2018; Gregory et al. 2017; Helfer et al. 2016). Nevertheless, meta-analysis suggests that the addition of antidepressant medications results in small beneficial effects on symptoms of depression, quality of life, and response rates as well as on positive symptoms, negative symptoms, and overall symptoms (Helfer et al. 2016). These effects were more prominent in patients with more severe depressive symptoms. Furthermore, antidepressant treatment did not appear to be associated with exacerbation of psychosis or significant differences in adverse effects (Helfer et al. 2016). Non-pharmacological treatments for depression in schizophrenia have been less well studied but could also be incorporated into treatment planning (Dondé et al. 2018; Opoka et al. 2017).

Treatments for posttraumatic stress disorder (Brand et al. 2018; Sin et al. 2017) and anxiety (Howells et al. 2017) in individuals with schizophrenia have been less well studied. Nevertheless, many individuals with schizophrenia will have experienced violent victimization (de Vries et al. 2019; Morgan et al. 2016; Roy et al. 2014) or childhood adversity (Bonoldi et al. 2013; Schalinski et al. 2017; Trotta et al. 2015; Varese et al. 2012) and the impact of these experiences will need to be considered as part of a patient-centered treatment plan (Center for Substance Abuse Treatment 2014). With anxiety symptoms in individuals with schizophrenia, the possible contributions of psychotic symptoms, medication side effects, substance intoxication or withdrawal, or co-occurring anxiety disorders may suggest an approach to treatment. Given the relative safety of adjunctive antidepressant medications in individuals with schizophrenia and depression, these medications may be considered if otherwise indicated to treat.
posttraumatic stress disorder or an anxiety disorder. On the other hand, studies on the use of benzodiazepines in schizophrenia are limited (Dold et al. 2012) and long-term use of benzodiazepines may be associated with increased risk of poorer outcomes, including side effects (Dold et al. 2013; Fond et al. 2018; Fontanella et al. 2016; Tiihonen et al. 2016) or development of a benzodiazepine use disorder (Maust et al. 2018). Non-pharmacological treatments for posttraumatic stress disorder in individuals with schizophrenia have been less well studied but may have modest benefits and do not appear to have significant adverse effects as compared to usual care (Brand et al. 2018; Sin et al. 2017).

In terms of the use of stimulants to treat pre-existing attention-deficit/hyperactivity disorder in individuals with schizophrenia, available evidence is also very limited but suggests a potential for worsening of psychotic symptoms as well as potential for development of a stimulant use disorder (Sara et al. 2014; Solmi et al. 2018a). Thus, if stimulant medications are used, monitoring for these possible adverse effects is warranted as part of the treatment plan.

The treatment plan should also give specific attention to concomitant non-psychiatric medical conditions such as diabetes, metabolic syndrome, obesity, sleep apnea, cardiovascular disease, or renal or hepatic disease that may influence treatment or monitoring recommendations. It is important that patients have access to primary care clinicians who can work with the psychiatrist to diagnose and treat concurrent physical health conditions, but the psychiatrist may also provide ongoing monitoring and treatment of common medical conditions in conjunction with primary care clinicians (Druss et al. 2018).

During pregnancy and the post-partum period, collaboration with the patient, her partner, and her obstetrician will be important in developing a plan of care aimed at optimizing outcomes for the patient and her infant.

In adapting treatment to the needs of the individual patient, tailoring of the treatment plan may also be needed based on sociocultural or demographic factors with an aim of enhancing quality of life or aspects of functioning (e.g., social, academic, occupational). Factors that influence medication metabolism (e.g., age, sex, body weight, renal or hepatic function, smoking status, use of multiple concurrent medications) may also require adjustments to the treatment plan, either in terms of typical medication doses or frequency of monitoring.

Strategies to promote adherence are always important to consider in developing a patient-centered treatment plan (Ferrando et al. 2014). Treatment planning to address adherence will depend on the specific contributing factors and whether reduced adherence is related to medication use, missed appointments, or other aspects of treatment. Potential factors that may influence adherence include the patient’s beliefs about the need for treatment, the perceived risks and benefits of treatment, barriers to treatment, and social support for adhering to treatment. Other issues that may need to be addressed to promote adherence include problems with the therapeutic alliance, limited insight into the presence of having an illness, general ambivalence about taking medications, cognitive impairments that affect remembering to take medications, distressing medication side effects (e.g., akathisia, sexual dysfunction), cultural or family beliefs about illness or treatment, or financial or insurance constraints on medications or visits. Transportation issues, lack of childcare, or work or school schedules may also pose barriers to attending appointments. Addressing these barriers as part of the treatment plan will require
active collaboration and problem-solving between the clinician and patient, often with input from the patient's family and others involved in their life. For example, to address difficulties adhering to medications, a LAI antipsychotic medication may be considered rather than oral medications (Kishimoto et al. 2018; Ingram et al. 2009), dosing can be adjusted to minimize side effects while maintaining efficacy, medication regimens can be simplified to reduce the number of pills or daily doses, watches or cell phone alarms can be used as reminders to take medications, pillboxes may be filled with the week's medication, and family or significant others may be enlisted to assist with medication if cognitive impairments are present. If financial issues with medications are affecting adherence, reassessment of the treatment regimen may be needed or patients’ assistance programs may be pursued (e.g., through pharmaceutical company programs or GoodRx: https://www.goodrx.com/). When a patient does not appear for appointments or is nonadherent in other ways, assertive outreach such as telephone calls or secure messages, may be helpful in reengaging the patient in treatment. For a small subgroup of patients with repeated relapses and rehospitalizations associated with nonadherence, mandatory outpatient treatment may warrant inclusion in the treatment plan to improve adherence and enhance outcomes (Kisely and Campbell 2015; Schneeberger et al. 2017).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

Development and documentation of a comprehensive, person-centered treatment plan assures that the clinician has considered the available nonpharmacological and pharmacological options for treatment and has identified those treatments that are best suited to the needs of the individual patient, with a goal of improving overall outcome. It may also assist in forming a therapeutic relationship, eliciting patient preferences, permitting education about possible treatments, setting expectations for treatment, and establishing a framework for shared decision making. Documentation of a treatment plan promotes accurate communication among all those caring for the patient and can serve as a reminder of prior discussions about treatment.

Harms

The only identifiable harm from this recommendation relates to the time spent in discussion and documentation that may reduce the opportunity to focus on other aspects of the evaluation.

Patient Preferences

Clinical experience suggests that patients are cooperative with and accepting of efforts to establish treatment plans.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. The level of research evidence is rated as low because no information is available on the harms of such an approach. There is also minimal research on whether developing and documenting a specific treatment plan improves outcomes as compared with assessment and documentation as usual. However, indirect evidence including expert opinion supports the benefits of comprehensive treatment planning. (For additional discussion of the research evidence, see Appendix C, Statement 3.)
Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Information from other guidelines (Addington et al. 2017a, 2017b; Barnes et al. 2011; Buchanan et al. 2010; Crockford and Addington 2017; Galletly et al. 2016; Hasan et al. 2012; Hasan et al. 2013; Hasan et al. 2015; National Institute for Health and Care Excellence 2014; Norman et al. 2017; Pringsheim et al. 2017; Scottish Intercollegiate Guidelines Network 2013) is generally consistent with this guideline statement in either explicitly or implicitly recommending development of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Quality Measurement Considerations

It is not known whether psychiatrists and other mental health professionals typically develop and document a comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments, and there is likely to be variability. As such, a well-defined and scientifically-sound quality measure could be developed to assess for the implementation of a person-centered treatment plan. Nevertheless, clinical judgment is needed to determine whether a documented treatment plan is comprehensive and person-centered. When developing such quality measures, specifications must address clinical interventions aimed at the treatment of schizophrenia, as well as consumer, caregiver, and evidence-based consensus about other person-centered aspects of treatment. Manual review of charts to evaluate for the presence of a person-centered treatment plan would be burdensome and time-consuming to implement. On the other hand, a quality measure could be electronically specified to assess for the presence or absence of specific text in the medical record that would reflect high-quality treatment planning. When considering the development of such electronically specified quality measures, there should be a thorough examination of the potential for unintended negative consequences, such as increased documentation burden or overuse of standardized language that meets the quality measure criteria but would inaccurately reflect what occurred in practice.

Electronic decision support related to the content of treatment plans would also be challenging to implement. However, in systems of care that require a formal interdisciplinary treatment plan at specified frequencies, electronic reminders may help assure timeliness of documentation.

Pharmacotherapy

Statement 4

APA recommends (1A) that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.*

* 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.
Implementation

Selection of an antipsychotic medication

General principles

In the treatment of schizophrenia, antipsychotic medication is one important component. The choice of an antipsychotic agent depends on many factors that are specific to an individual patient. Thus, before initiating treatment with antipsychotic medication, it is recommended that the treating clinician gather information on the patient's treatment-related preferences and prior treatment responses and then discuss the potential benefits and risks of medication options with the patient. The depth of this discussion will, of course, be determined by the patient's condition. Even with agitated patients and patients with thought disorder, however, the therapeutic alliance will be enhanced if the patient and physician can identify target symptoms (e.g., anxiety, poor sleep, and, for patients with insight, hallucinations and delusions) that are subjectively distressing and that antipsychotics can ameliorate. Mentioning the possibility of acute side effects (e.g., dizziness, sedation, restlessness) helps patients to identify and report their occurrence and also may help maintain a therapeutic alliance. Patients with schizophrenia often have attentional and other cognitive impairments that may be more severe during an acute illness exacerbation, and so it is helpful to return to the topic of identification of target symptoms and discussion of acute and longer-term side effects on multiple occasions as treatment proceeds.

An evidence-based listing of first-generation antipsychotic medications (FGAs) and second-generation antipsychotic medications (SGAs) or an algorithmic approach to antipsychotic selection is not possible because of the significant heterogeneity in clinical trial designs, the limited numbers of head to head comparisons of antipsychotic medications, and the limited clinical trial data for a number of the antipsychotic medications. Although there may be clinically meaningful distinctions in response and tolerability of different antipsychotic medications in an individual patient, there is no definitive evidence that one antipsychotic will have consistently superior efficacy compared with another. Furthermore, there is no reliable strategy to predict response or risk of side effects with one agent compared with another. Consequently, the choice of a particular antipsychotic agent is typically based on patient preferences, the patient's past responses to treatment (including symptom response and tolerability), the medication's side effect profile (see Table 6), the presence of physical health conditions that may be affected by medication side effects, and other medication related factors such as available formulations, potential for drug-drug interactions, receptor binding profiles, and pharmacokinetic considerations. (See Tables 3 to 9.)
**Table 3. Antipsychotic medications: available formulations and dosing considerations**

<table>
<thead>
<tr>
<th>Trade Name&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
<th>Initial dose (mg/day)</th>
<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments&lt;sup&gt;6,7,8&lt;/sup&gt;</th>
</tr>
</thead>
</table>

**First-Generation Antipsychotics**

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1. This table and subsequent medication-related tables include information compiled from multiple sources. It is recommended that readers consult product labeling information for authoritative information on these medications. Detailed information on issues such as dose regimen, dose adjustments, medication administration procedures, handling precautions, and storage can also be found in product labeling.

2. Long-acting injectable formulations of antipsychotic medications are described separately in Tables 7, 8, and 9. Droperidol is a first-generation antipsychotic medication but is not included because it is only available in a parenteral formulation for short-term use, primarily for treatment of agitation or post-operative nausea and vomiting. Pimavanserin is a second-generation antipsychotic but is not included as it is FDA-indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis. Mesoridazine and triflupromazine were previously marketed in the U.S. but are no longer available. Other antipsychotic medications and other formulations of the listed medications may be available in Canada.


4. Source. Package insert references:
   - Abilify 2017; Abilify 2018; Abilify Maintena 2018; Abilify Mycite 2017; Aristada 2018; Aristada Initio 2018; Chlorpromazine Hydrochloride Injection 2010; Chlorpromazine Hydrochloride Injection 2018; Clozapine 2017; Clozapine (clozapine) 2017; Clozapine (clzapoxine) 2018; Fanapt (iloperidone) 2017; Fluphenazine decanoate injection 2018; Fluphenazine hydrochloride elixir 2010; Fluphenazine hydrochloride injection 2010; Fluphenazine hydrochloride solution, concentrate 2010; Fluphenazine hydrochloride tablets 2016; Geodon (ziprasidone) 2018; Haldo decanoate injection (haloperidol) 2017; Haldo lactate injection (haloperidol) 2017; Haloperidol lactate injection 2011; Haloperidol lactate oral solution 2016; Haloperidol tablets 2015; Invega (paliperidone) 2010; Invega (palipernone) 2019; Invega Sustenn (paliperidone) July 2018; Invega Sustenn (paliperidone) September 2018; Invega Trinza (paliperidone) July 2018; Invega Trinza (paliperidone) September 2018; Latuda (lurasidone) 2017; Loxitane (loxapine) 2017; Loxapac (loxapine hydrochloride) 2014; Navane (thiothixene) 2010; Nuplazid (10 and 34 mg pimavanserin) 2018; Nuplazid (17 mg pimavanserin) 2018; Orap (pimozide) 2019; Orap (ziprasidone) 2019; Perphenazine 2016; Perzip (atenolol) 2018; Rexulti (brexpiprazole) 2018; Risperdal (risperidone) 2017; Risperdal Consta 2017; Saphris (asenapine) February 2017; Saphris (asenapine) January 2017; Seroquel (quetiapine) 2018; Seroquel XR (quetiapine) 2018; Thioridazine hydrochloride 2018; Trifluoperazine 2011; Vraylar (cariprazine) 2018; Zyprexa (olanzapine) March 2018; Zyprexa Relprev (olanzapine) 2018

5. The most common U.S. trade names are included for reference only. At the time of publication, some of these products may only be manufactured as generic products.

6. Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo and an FDA black box warning applies to all antipsychotic medications. Antipsychotic agents with an indication for augmentation treatment in major depressive disorder (e.g., aripiprazole, brexpiprazole) have an additional black box warning related to increased risk of suicidal thinking/behaviors.

7. May be taken without regard to food or other medications unless specifically noted.

8. Tablets are able to be crushed or split unless specifically noted.
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
<th>Initial dose (mg/day)</th>
<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine Tablet: 10, 25, 50, 100, 200 Short-acting injection (HCl): 25/mL (1 mL); 50/2 mL (2 mL)</td>
<td>25-100</td>
<td>200 – 800</td>
<td>Oral: 1000-2000</td>
<td>Intramuscular (IM) dosing is typically 25-50 mg per upper outer quadrant of gluteal with 200 mg/day maximum; do not inject subcutaneously; use much lower IM doses than oral doses as oral first-pass metabolism is significant.</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolxin Tablet: 1, 2.5, 5, 10 Oral Concentrate: 5/mL (120 mL) Short-acting injection (HCl): 2.5/mL (10 mL)</td>
<td>2.5 - 10</td>
<td>6 - 20</td>
<td>Oral: 40 IM: 10</td>
<td>Short-acting IM dose is 33-50% of oral dose. Dilute oral concentrate immediately before use to ensure palatability and stability.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol Tablet: 0.5, 1, 2, 5, 10, 20 Oral Concentrate: 2/mL (5 mL, 15 mL, 120 mL) Short-acting injection (lactate): 5/mL (1 mL, 10 mL)</td>
<td>1 - 15</td>
<td>5 - 20</td>
<td>100</td>
<td>2-5 mg IM can be given every 4-8 hours. IV administration has been associated with QTc prolongation and ECG monitoring is recommended.</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane Capsule: 5, 10, 25, 50 Aerosol Powder Breath Activated Inhalation: 10</td>
<td>20</td>
<td>60 -100a</td>
<td>250</td>
<td>Oral inhalation formulation (Adasuve) to treat agitation requires REMS program due to potential for bronchospasm.</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban Tablet: 5, 10, 25</td>
<td>50 - 75</td>
<td>30 – 100a</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon Tablet: 2, 4, 8, 16</td>
<td>8 - 16</td>
<td>8 - 32</td>
<td>64</td>
<td>CYP2D6 poor metabolizers will have higher plasma concentrations</td>
</tr>
</tbody>
</table>

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9 Usually given in divided doses.
### Trade Name

**Initial dose**

**Typical dose range**

**Maximum daily dose**

**Comments**

<table>
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<tr>
<th>Trade Name</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
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<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimozide</td>
<td>Orap [Tablet: 1, 2]</td>
<td>0.5 - 2</td>
<td>2 - 4</td>
<td>10</td>
<td><em>Sometimes used off-label to treat delusional disorders such as delusional parasitosis. Perform CYP2D6 genotyping if doses greater than 4 mg/day are used. In poor CYP2D6 metabolizers, do not give more than 4 mg/day and do not increase dose earlier than 14 days.</em></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril [Tablet: 10, 25, 50, 100]</td>
<td>150 - 300</td>
<td>300 – 800(^6)</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane [Capsule: 1, 2, 5, 10]</td>
<td>6 - 10</td>
<td>15-30</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine [Tablet: 1, 2, 5, 10]</td>
<td>4 - 10</td>
<td>15-20</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

### Second-Generation Antipsychotics

<p>| Aripiprazole | Abilify [Tablet: 2, 5, 10, 15, 20, 30]               | 10 -15               | 10-15                       | 30                         | <em>Adjust dose if a poor CYP2D6 metabolizer or with concomitant use of a CYP3A4 inhibitor, CYP3A4 inducer, or CYP2D6 inhibitor. Tablet and oral solution may be interchanged on a mg-per-mg basis, up to 25 mg. Doses using 30 mg tablets should be exchanged for 25 mg oral solution. Orally disintegrating tablets (Abilify Discmelt) are bioequivalent to the immediate-release tablets (Abilify). Mycite patch (wearable sensor) cannot be split or crushed.</em> |</p>
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
<th>Initial dose (mg/day)</th>
<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asenapine</td>
<td>Saphris Tablet, Sublingual: 2.5, 5, 10</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>Consider dose adjustment in smokers and with concomitant use of CYP1A2 inhibitors. Do not split, crush, or swallow. Place under tongue and allow to dissolve completely. Giving with food or liquid reduces absorption.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti Tablet: 0.25, 0.5, 1, 2, 3, 4</td>
<td>1</td>
<td>2 - 4</td>
<td>4</td>
<td>Adjust dose if a poor CYP2D6 metabolizer or with concomitant use of moderate/strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, or strong CYP3A4 inducers</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar Capsule: 1.5, 3, 4.5, 6</td>
<td>1.5</td>
<td>1.5 - 6</td>
<td>6&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Adjust dose with concomitant use of a strong CYP3A4 inhibitor or inducer.</td>
</tr>
</tbody>
</table>

<sup>10</sup> Up to 9 mg/d has been studied in clinical trials.
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
<th>Initial dose (mg/day)</th>
<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril; FazaClo; Versacloz Tablet: 25, 50, 100, 200 Tablet, Disintegrating: 12.5, 25, 100, 150, 200 Oral Suspension: 50/mL (100 mL)</td>
<td>12.5 – 25</td>
<td>300 - 450$^7$</td>
<td>900</td>
<td>Prescribers must complete Clozapine REMS education (<a href="https://www.clozapinerems.com/">https://www.clozapinerems.com/</a>) and follow requirements for a baseline CBC and ANC, and for ANC monitoring before and during treatment. When initiating clozapine, increase in 25-50 mg/d increments for 2 weeks, then further increments not exceeding 100 mg up to twice weekly. For treatment interruptions of 2 or more days, restart at 12.5 mg once or twice daily. Re-titration can occur more rapidly than with initial treatment. Adjust dose with concomitant use of strong CYP1A2 inhibitors and with strong CYP3A4 inducers. Smoking reduces clozapine levels via CYP1A2 induction. Clozapine levels can be informative in making dose adjustments.$^{11}$</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt Tablet: 1, 2, 4, 6, 8, 10, 12</td>
<td>2</td>
<td>12-24</td>
<td>24</td>
<td>Titrate slowly (no more than 4 mg/d increase in dose); follow initial titration approach if more than 3-day gap in treatment; adjust dose with concomitant use of strong CYP2D6 or CYP3A4 inhibitors and reduce dose by 50% in CYP2D6 poor metabolizers.</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda Tablet: 20, 40, 60, 80, 120</td>
<td>40</td>
<td>40-120</td>
<td>160</td>
<td>Administer with food (≥350 calories). Adjust dose for concomitant use of moderate to strong CYP3A4 inhibitors or inducers.</td>
</tr>
</tbody>
</table>

$^{11}$ Clozapine levels should be drawn after at least 3 days on a stable dose and about 12 hours after the last dose. Levels associated with efficacy show individual variation but typically efficacy begins at a level above 250 ng/ml with the most efficacy seen at levels higher than 350 ng/ml. The risk of developing seizures increases with levels above 1000 mcg/L. Levels of the active metabolite, norclozapine, should be considered when interpreting clozapine levels.
| Trade Name | Available Preparations (mg, unless otherwise noted) | Initial dose (mg/day) | Typical dose range (mg/day) | Maximum daily dose (mg/day) | Comments
---|---|---|---|---|---
Olanzapine | Zyprexa Table: 2.5, 5, 7.5, 10, 15, 20 Tablet, Disintegrating: 5, 10, 15, 20 Short-acting Intramuscular Powder for Solution: 10 | 5-10 | 10-20 | 20 | Short-acting IM preparation is used primarily for agitation with usual dose of 2.5-10 mg IM, with max dose of 30 mg/day. Administer IM slowly, deep into muscle. Do not use subcutaneously. Concomitant use of IM olanzapine with benzodiazepines is not recommended. Smokers may require a 30% greater daily dose than nonsmokers and women may need lower daily doses. ~40% of an oral dose is removed by first pass metabolism as compared to IM dose. IM elimination half-life is ~1.5 times greater in elderly. Oral dissolving tablet dissolves rapidly in saliva and may be swallowed with or without liquid. May be administered with or without food/meals.
Paliperidone | Invega Tablet, Extended Release: 1.5, 3, 6, 9 | 6 | 3 - 12 | 12 | If exceeding 6 mg daily, increases of 3 mg/day are recommended at intervals of more than 4 days, up to a max of 12 mg/d. Uses OROS osmotic delivery system for tablet; do not split or crush. Use of extended release tablet is not recommended with preexisting severe gastrointestinal narrowing disorders. Tablet shell is expelled in the stool.

12 Olanzapine has been used at higher doses, typically up to 30 mg/d, although some case series describe use of up to 60 mg/d.
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Available Preparations (mg, unless otherwise noted)</th>
<th>Initial dose (mg/day)</th>
<th>Typical dose range (mg/day)</th>
<th>Maximum daily dose (mg/day)</th>
<th>Comments&lt;sup&gt;5,7,8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>Seroquel Tablet, Immediate Release: 25, 50, 100, 200, 300, 400 Tablet, Extended Release: 50, 150, 200, 300, 400</td>
<td>IR: 50 XR: 300</td>
<td>IR/XR: 400-800</td>
<td>IR/XR: 800</td>
<td>Once daily dosing for extended release and divided dosing for immediate release. Do not split or crush extended release tablets. Immediate release marginally affected by food, whereas extended release significantly affected with high-fat meal. Give extended release tablets without food or &lt;300 calories. Re-titrates for gap in treatment of more than 1 wk. Adjust dose for concomitant use of strong CYP3A4 inhibitors or inducers.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal Tablet: 0.25, 0.5, 1, 2, 3, 4 Tablet, Disintegrating: 0.25, 0.5, 1, 2, 3, 4 Oral Solution: 1/mL (30 mL)</td>
<td>2</td>
<td>2 - 8</td>
<td>8&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Lower initial doses and slower titration rates with severe hepatic impairment or CrCl &lt;30 mL/min. Fraction of free risperidone is increased with hepatic impairment. Adjust dose with concomitant use of inducers or inhibitors of CYP3A4 or CYP2D6. Check labeling for compatible liquids with oral solution. Do not split or crush oral disintegrating tablets.</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon Capsule: 20, 40, 60, 80 Solution Reconstituted, Intramuscular: 20</td>
<td>40</td>
<td>80 – 160</td>
<td>320</td>
<td>Give capsules with &gt;500 calories of food. No data suggests improved efficacy at higher doses. See labeling for reconstitution and storage of IM preparation. Short-acting IM preparation is used primarily for agitation with usual dose of 20 mg/day and max dose of 40 mg/day.</td>
</tr>
</tbody>
</table>

<sup>13</sup> Doses of risperidone up to 16 mg/day have been studied in clinical trials; however, doses >6 mg do not appear to confer additional benefit and have a higher incidence of extrapyramidal symptoms than lower doses.
Table 4. Antipsychotic medications: pharmacokinetics/pharmacodynamics\(^\text{14}\)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Bioavailability</th>
<th>Time to peak level</th>
<th>Protein binding</th>
<th>Metabolic enzymes/transporters</th>
<th>Metabolites</th>
<th>Elimination half-life</th>
<th>Excretion</th>
<th>Hepatic Impairment</th>
<th>Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>32%</td>
<td>2.8 hours</td>
<td>90 - 99%</td>
<td>CYP2D6 (Major), CYP1A2 (Minor), CYP3A4 (Minor) substrate</td>
<td>NOR2CPZ, NOR2CPZ SULF, and 3-OH CPZ</td>
<td>Biphasic: initial 2 hours, terminal 30 hours</td>
<td>Primarily renal (&lt;1% as unchanged drug)</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>2.7%</td>
<td>Oral: 2 hours</td>
<td>99%</td>
<td>CYP2D6 (Major) substrate</td>
<td>7-hydroxyfluphenazine, fluphenazine-sulfoxide</td>
<td>4.4 to 16.4 hours</td>
<td>Renal and fecal; exact proportion unclear</td>
<td>Contraindicated by manufacturer</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>60-70%</td>
<td>Oral: 2-6 hours</td>
<td>89-93%</td>
<td>CYP2D6 (Major), CYP3A4 (Major), CYP1A2 (Minor) substrate; 50-60% glucuronidation</td>
<td>Hydroxymetabolite-reduced haloperidol</td>
<td>14 to 37 hours</td>
<td>15% fecal; 30% renal (1% as unchanged drug); + enterohepatic circulation</td>
<td>No dose adjustments noted</td>
</tr>
</tbody>
</table>

\(^{14}\) Source. Hiemke et al. 2018; Koytchev et al. 1996; Lexicomp 2019; Micromedex 2019; Mountjoy et al. 1999; Procyshyn et al. 2019; Vermeir et al. 2008
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Bioavailability</th>
<th>Time to peak level</th>
<th>Protein binding</th>
<th>Metabolic enzymes/transporters</th>
<th>Metabolites</th>
<th>Elimination half-life</th>
<th>Excretion</th>
<th>Hepatic Impairment</th>
<th>Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
<td>99%</td>
<td>1.5 - 3 hours</td>
<td>97% CYP1A2 (Minor), CYP2D6 (Minor), CYP3A4 (Minor) substrate, P-glycoprotein inhibitor</td>
<td>N-desmethyl loxapine (amoxapine), 8-hydroxyloxapine</td>
<td>Biphasic: initial 5 hours, terminal 19 hours</td>
<td>Renal and fecal</td>
<td>No dose adjustments noted</td>
<td>No dose adjustments noted</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban</td>
<td>Unclear</td>
<td>1.5 hours</td>
<td>76% CYP2D6</td>
<td>Multiple</td>
<td>1.5 hours</td>
<td>Renal and fecal</td>
<td>Use with caution</td>
<td>No dose adjustments noted</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
<td>20 - 40%</td>
<td>Perphenazine: 1 - 3 hours, 7-hydroxyperphenazine: 2 - 4 hours</td>
<td>91-99% CYP2D6 (Major) substrate, CYP1A2 (Minor), CYP2C19 (Minor), CYP2C9 (Minor), CYP3A4 (Minor) substrate</td>
<td>7-hydroxyperphenazine (responsible for 70% of the activity)</td>
<td>Perphenazine: 9-12 hours, 7-hydroxyperphenazine: 10-19 hours</td>
<td>5% fecal; 70% renal</td>
<td>Contraindicated in liver damage</td>
<td>Use with Caution</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap</td>
<td>≥50%</td>
<td>6 - 8 hours</td>
<td>99% CYP1A2 (Major), CYP2D6 (Major), CYP3A4 (Major) substrate</td>
<td>Unknown activity: 4-bis-(4-fluorophenyl) butyric acid, 1-(4-piperidyl)-2-benzimidazolinone</td>
<td>55 hours</td>
<td>Primarily renal</td>
<td>Use with caution</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
<td>25-33%</td>
<td>1 - 4 hours</td>
<td>96-99% CYP2D6 (Major) substrate and moderate inhibitor, CYP2C19 (Minor) substrate</td>
<td>Mesoridazine (twice as potent as thioridazine), sulphoridazine</td>
<td>21-24 hours</td>
<td>Minimal renal</td>
<td>Use with caution</td>
<td>No dose adjustments noted</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
<td>Metabolites</td>
<td>Elimination half-life</td>
<td>Excretion</td>
<td>Hepatic Impairment</td>
<td>Renal Impairment</td>
</tr>
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<td>-----------------</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
<td>~50%; erratic absorption</td>
<td>1 - 2 hours</td>
<td>90%</td>
<td>CYP1A2 (Major) substrate</td>
<td>None noted</td>
<td>34 hours</td>
<td>Feces (unchanged drug and metabolites)</td>
<td>No dose adjustments noted</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>Erratic absorption</td>
<td>1.5 - 6 hours</td>
<td>90-99%</td>
<td>CYP1A2 (Major) substrate</td>
<td>N-desmethyltrifluoperazine, 7-hydroxytrifluoperazine, and other metabolites</td>
<td>3 - 12 hours</td>
<td>Renal</td>
<td>Contraindicated in hepatic disease</td>
</tr>
</tbody>
</table>

**Second-Generation Antipsychotics**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Bioavailability</th>
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<th>Renal Impairment</th>
</tr>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>87%</td>
<td>3 - 5 hours</td>
<td>&gt;99%</td>
<td>CYP2D6 (Major), CYP3A4 (Major) substrate</td>
<td>Dehydro-aripiprazole</td>
<td>75 hours; 94 hours dehydro-aripiprazole 146 hours in poor CYP2D6 metabolizers</td>
<td>55% fecal 25% renal</td>
<td>No dose adjustments noted</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
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<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>35%</td>
<td>0.5 - 1.5 hours</td>
<td>95%</td>
<td>CYP1A2 (Major), CYP2D6 (Minor), CYP3A4 (Minor) substrate; glucuronidation by UGT1A4; CYP2D6 weak inhibitor</td>
<td>Inactive: N(+)-glucuronide, N-desmethylasenapine, and N-desmethylasenapine N-carbamoyl glucuronide</td>
<td>24 hours</td>
<td>40% fecal</td>
<td>Use is contraindicated in severe hepatic impairment (Child-Pugh class C)</td>
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<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>95%</td>
<td>4 hours</td>
<td>&gt;99%</td>
<td>CYP3A4 (Major), CYP2D6 (Major) substrate</td>
<td>Inactive: DM-3411</td>
<td>91 hours</td>
<td>46% fecal</td>
<td>Moderate - severe impairment (Child-Pugh class B or C) Maximum dose: MDD: 2 mg/day Schizophrenia: 3 mg/day</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>High</td>
<td>3-6 hours</td>
<td>91-97%</td>
<td>CYP3A4 (Major), CYP2D6 (Minor) substrate</td>
<td>Desmethyl cariprazine [DCAR], didesmethyl cariprazine [DDCAR]</td>
<td>Cariprazine 2 - 4 days DCAR: 1-2 days DDCAR: 1-3 weeks</td>
<td>21% renal</td>
<td>Severe impairment (Child-Pugh class C): not recommended</td>
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<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
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<td>Elimination half-life</td>
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<td>Renal Impairment</td>
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</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril; FazaClo; Versacloz</td>
<td>27 - 60% (range: 1-6 hours)</td>
<td>97%</td>
<td>CYP1A2 (Major), CYP2A6 (Minor), CYP2C19 (Minor), CYP2C9 (Minor), CYP2D6 (Minor), CYP3A4 (Minor) substrate</td>
<td>N-desmethylclozapine (active), hydroxylated and n-oxide derivatives (inactive)</td>
<td>4 – 66 hours (steady state 12 hours)</td>
<td>30% fecal 50% renal</td>
<td>In significant impairment, dose reduction may be necessary</td>
<td>In significant impairment, dose reduction may be necessary</td>
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<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
<td>96%</td>
<td>2 - 4 hours</td>
<td>CYP2D6 (Major), CYP3A4 (Minor) substrate, CYP3A4 weak inhibitor</td>
<td>P88 P95</td>
<td>Extensive metabolizers: Iloperidone 18 hours, P88 26 hours, P95 23 hours Poor metabolizers: Iloperidone 33 hours, P88 37 hours, P95 31 hours</td>
<td>~20% fecal ~50% renal</td>
<td>Moderate impairment: use with caution Severe impairment: not recommended</td>
<td>No dose adjustments noted</td>
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<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
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<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>9-19%</td>
<td>1-3 hours</td>
<td>CYP3A4 (Major) substrate, CYP3A4 weak inhibitor</td>
<td>ID-14283, ID-14326 (active); ID20219, ID-20220 (inactive)</td>
<td>Lurasidone 18-40 hours; ID-14283: 7.5-10 hours</td>
<td>~80% fecal</td>
<td>For moderate to severe hepatic impairment (Child-Pugh class B and class C) use 20 mg/day initially with maximum dose of 80 mg/day and 40 mg/day, respectively</td>
<td>For CrCl &lt; 50 mg/min: initial 20 mg/day, maximum dose is 80 mg/day</td>
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<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>&gt;57%</td>
<td>Oral: 6 hours IM: 15-45 mins</td>
<td>CYP1A2 (Major), CYP2D6 (Minor) substrate; metabolized via direct glucuronidation</td>
<td>10-N-glucuronide, 4-N-desmethyl olanzapine (inactive)</td>
<td>30 hours</td>
<td>30% fecal</td>
<td>Use with caution</td>
<td>Not removed by dialysis</td>
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<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
<td>Metabolites</td>
<td>Elimination half-life</td>
<td>Excretion</td>
<td>Hepatic Impairment</td>
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<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>28%</td>
<td>24 hours</td>
<td>74%</td>
<td>P-glycoprotein/ABCB1, CYP2D6(Minor), CYP3A4 (Minor) substrate</td>
<td>Activity unclear: M1, M9, M10, M11, M12, M16</td>
<td>23 hours; 24-51 hours with renal impairment (CrCl &lt;80ml/min)</td>
<td>11% fecal</td>
<td>80% renal</td>
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<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>100%</td>
<td>Immediate release: 1.5 hours; Extended release: 6 hours</td>
<td>83%</td>
<td>CYP3A4 (Major), CYP2D6 (Minor) substrate</td>
<td>Active: Norquetiapine, 7-hydroxyquetiapine Inactive: quetiapine sulfoxide (Major), parent acid metabolite</td>
<td>Quetiapine: 6 - 7 hours Norquetiapine: 12 hours</td>
<td>20% fecal</td>
<td>73% renal</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
<td>Metabolites</td>
<td>Elimination half-life</td>
<td>Excretion</td>
<td>Hepatic Impairment</td>
<td>Renal Impairment</td>
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</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal 70 - 94%</td>
<td>1 hour</td>
<td>90%</td>
<td>CYP2D6 (Major), CYP3A4 (Minor), P-glycoprotein/ABCB1 substrate, N-dealkylation (minor), CYP2D6 weak inhibitor</td>
<td>Active: 9-hydroxy-risperidone</td>
<td>Risperidone 3 - 20 hours</td>
<td>14% fecal</td>
<td>Mild or moderate impairment (Child-Pugh class A or B): reduce dose</td>
<td>Mild or moderate impairment (CrCl ≥30 mL/min): reduce dose</td>
</tr>
<tr>
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<td></td>
<td>9-hydroxy-risperidone 21 – 30 hours</td>
<td>90% renal</td>
<td>Severe impairment (Child-Pugh class C): initial 0.5 mg twice a day, increase by no more than 0.5 mg twice a day, may increase to total dosage &gt; 1.5 mg twice a day at 1 week or greater</td>
<td>Severe impairment (CrCl &lt;30 mL/min): initial 0.5 mg twice a day, increase by no more than 0.5 mg twice a day, may increase to dosage &gt; 1.5 mg twice a day at 1 week or greater</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Bioavailability</td>
<td>Time to peak level</td>
<td>Protein binding</td>
<td>Metabolic enzymes/transporters</td>
<td>Metabolites</td>
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</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>Oral with food: 60%; IM: 100%</td>
<td>Oral: 6 - 8 hours IM: 60 mins</td>
<td>CYP1A2 (Minor), CYP3A4 (Minor) substrate, glutathione, aldehyde oxidase</td>
<td>Active: benzisothiazole sulphoxide (Major), benzisothiazole sulphone (Major), ziprasidone sulphoxide, s-methyl-dihydroziprasidone</td>
<td>Oral: 7 hours; IM: 2 – 5 hours</td>
<td>66% fecal 20% renal</td>
<td>No oral dose adjustments noted; IM formulation contains a renally cleared excipient, cyclodextrin - use with caution.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Antipsychotic receptor binding properties**\(^{15}\)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>5HT-1A</th>
<th>5HT-2A</th>
<th>5HT-2C</th>
<th>5HT-7</th>
<th>H1</th>
<th>Musc</th>
<th>Alpha 1</th>
<th>Alpha 2</th>
<th>Comments</th>
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<tr>
<td><strong>First-Generation Antipsychotics</strong></td>
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\(^{15}\) **Source.** Allergan 2019a, 2019b; Lexicomp 2019; Maeda et al. 2014; Micromedex 2019; Olten and Bloch 2018; Otsuka 2019; PDSP Ki database 2019; Procyshyn et al. 2019; Roth et al. 2000; Sunovion 2019
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<th>D3</th>
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<th>5HT-2A</th>
<th>5HT-2C</th>
<th>5HT-7</th>
<th>H1</th>
<th>Musc</th>
<th>Alpha 1</th>
<th>Alpha 2</th>
<th>Comments</th>
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**Second-Generation Antipsychotics**

<p>| Aripiprazole | Abilify | + | /// | +++ | + | 0 | /// | +++ | ++ | ++ | ++ | 0 | ++ | + |
| Asenapine    | Saphris  | +++| +++| +++| +++| +++| +++| +++| +++| +++| 0 | +++| +++| + |
| Brexpiprazole| Rexulti  | + | /// | +++| +++| +++| +++| +++| ++ | +++| 0 | +++| +++| +++ |
| Cariprazine  | Vraylar  | /// | +++| +++| ++ | +  | +  | ++ | 0  | +  | +  | +  | +  | +  |
| Clozapine    | Clozaril; FazaClo; Versacloz | + | + | + | ++ | + | /// | +++| ++ | ++ | +++| ///| +++| + |
| Iloperidone  | Fanapt   | + | ++ | ++ | ++ | + | /// | +++| ++ | ++ | 0 | +++| +++| + |
| Lurasidone   | Latuda   | + | +++| ++ | ++ | + | /// | +++| +  | +++| 0 | 0  | ++ | ++ | + |</p>
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
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**** = very strong binding (Ki < 1 nM); +++ = strong binding (1 nM ≤ Ki < 10 nM); ++ = moderate binding (10 nM ≤ Ki < 100 nM); + = weak binding (100 nM ≤ Ki < 1000 nM); 0 = very weak or negligible binding (Ki ≥ 1000 nM). For partial agonists, / is used to denote relative binding values instead of +.

### Table 6. Antipsychotic medications: relative side effects

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Akathisia</th>
<th>Parkinsonism</th>
<th>Dystonia</th>
<th>Tardive dyskinesia</th>
<th>Hyperprolactinemia</th>
<th>Anticholinergic</th>
<th>Sedation</th>
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<td>Chlorpromazine</td>
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</tbody>
</table>


17 In general, rates of sexual dysfunction parallel rates of hyperprolactinemia except where noted in comments.
<table>
<thead>
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<th>Trade Name</th>
<th>Trade Name</th>
<th>Akathisia</th>
<th>Parkinsonism</th>
<th>Dystonia</th>
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**Second-Generation Antipsychotics**

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<th>Trade Name</th>
<th>Trade Name</th>
<th>Akathisia</th>
<th>Parkinsonism</th>
<th>Dystonia</th>
<th>Tardive dyskinesia</th>
<th>Hyper-prolactinemia</th>
<th>Anticholinergic</th>
<th>Sedation</th>
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<td>+</td>
<td>+</td>
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<td>++</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>Clozaril; FazaClo; Versacloz</td>
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Table 6. Antipsychotic medications: relative side effects (continued)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Seizures</th>
<th>Orthostasis</th>
<th>QT prolongation</th>
<th>Weight gain</th>
<th>Hyperlipidemia</th>
<th>Glucose abnormalities</th>
<th>Comments</th>
</tr>
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<tr>
<td><strong>First-Generation Antipsychotics</strong></td>
<td></td>
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<td>Thiothixene</td>
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<tr>
<td>Trade Name</td>
<td>Seizures</td>
<td>Orthostasis</td>
<td>QT prolongation</td>
<td>Weight gain</td>
<td>Hyperlipidemia</td>
<td>Glucose abnormalities</td>
<td>Comments</td>
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**Second-Generation Antipsychotics**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Seizures</th>
<th>Orthostasis</th>
<th>QT prolongation</th>
<th>Weight gain</th>
<th>Hyperlipidemia</th>
<th>Glucose abnormalities</th>
<th>Comments</th>
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</thead>
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<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>FDA safety alert for impulse control disorders (e.g., gambling, binge eating); may reduce hyperprolactinemia with other antipsychotics</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Oral hypoesthesia</td>
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<td>Brexpiprazole</td>
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<td>+</td>
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<td>++</td>
<td></td>
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<td>Cariprazine</td>
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<td>+</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril;</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Increased salivation common; high rate of sexual dysfunction; severe constipation possible; severe constipation possible; fever can occur with initiation; myocarditis and agranulocytosis are rare.</td>
</tr>
<tr>
<td></td>
<td>FazaClo;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>Versacloz</td>
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<td>++</td>
<td>++</td>
<td>+</td>
<td>Dose-related creatinine increase in some patients</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>Dose-related creatinine increase in some patients</td>
</tr>
<tr>
<td>Olanzapine</td>
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<td>Paliperidone</td>
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<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
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<td>++</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Intraoperative floppy iris syndrome reported</td>
</tr>
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</table>
Table 7. Long-acting injectable antipsychotic medications: availability and injection related considerations

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Seizures</th>
<th>Orthostasis</th>
<th>QT prolongation</th>
<th>Weight gain</th>
<th>Hyperlipidemia</th>
<th>Glucose abnormalities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
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<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

1215

This table and the subsequent table on long-acting injectable antipsychotic medications include information compiled from multiple sources. It is recommended that readers consult product labeling information for authoritative information on these medications. Detailed information on issues such as dose regimen, dose adjustments, medication administration procedures, appropriate needle size based on injection site and patient weight, product reconstitution, handling precautions, and storage can also be found in product labeling.


19 Available strengths are based on U.S. products; strengths and products available in other countries may differ.

20 Long-acting injectable antipsychotic medications should never be administered intravenously.

21 Pain at injection site noted for all products.


<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Available strengths (mg)</th>
<th>How supplied</th>
<th>Injection site and technique</th>
<th>Reactions at injection site</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol Haldol Decanoate</td>
<td>50/mL, 100/mL</td>
<td>Vial, Sesame oil vehicle with 1.2% benzyl alcohol</td>
<td>Deep IM gluteal or deltoid injection; use of Z-track technique recommended</td>
<td>Inflammation and nodules reported, especially with dose &gt; 100 mg/ml</td>
<td>Do not administer more than 3 mL per injection site. In sesame oil; be alert for allergy. Needle size issues – refer to labelling.</td>
</tr>
<tr>
<td>Aripiprazole Abilify Maintena</td>
<td>300, 400</td>
<td>Kit with either pre-filled syringe or single use vial</td>
<td>Slow IM injection into gluteal or deltoid muscle</td>
<td>Occasional redness, swelling, induration (mild to moderate)</td>
<td>Rotate injection sites; do not massage muscle after injection. Needle size and reconstitution issues – refer to labelling.</td>
</tr>
<tr>
<td>Aripiprazole lauroxil Aristada Initiio (for first dose) and Aristada</td>
<td>675/2.4 mL, Aristada 441/1.6 mL, 662/2.4 mL, 882 /3.2 mL, 1064/3.9 mL</td>
<td>Kit with pre-filled syringe</td>
<td>IM gluteal muscle; Aristada Initiio 675 mg and Aristada 441 mg can be injected in deltoid muscle</td>
<td>Infrequent induration</td>
<td>Avoid concomitant injection of Aristada Initiio and Aristada in same muscle. Needle size and reconstitution issues – refer to labelling.</td>
</tr>
<tr>
<td>Olanzapine Zyprexa Relprevv</td>
<td>210, 300, 405</td>
<td>Kit with vial containing diluent and vial with powder for reconstituting suspension</td>
<td>Deep IM gluteal injection only; do not administer subcutaneously</td>
<td>Infrequent induration or mass at injection site</td>
<td>Due to risk of post-injection delirium/sedation syndrome, must be given in a registered healthcare facility with ready access to emergency response services, and patient must be observed for at least 3 hours post injection and accompanied upon discharge. Requires use of FDA REMS program (<a href="http://www.zyprxarelprevvprogram.com/public/Default.aspx">www.zyprxarelprevvprogram.com/public/Default.aspx</a>). Do not massage muscle after injection. The combined effects of age, smoking, and gender may lead to significant pharmacokinetic differences. Handling and reconstitution issues – refer to labelling.</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Available strengths(^{20}) (mg)</td>
<td>How supplied</td>
<td>Injection site and technique(^{21})</td>
<td>Reactions at injection site(^{22})</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------</td>
<td>--------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Sustenna</td>
<td>39/0.25 mL, 78/0.5 mL, 117/0.75 mL, 156/mL, 234/1.5 mL</td>
<td>Kit with Pre-filled syringe</td>
<td>IM only; Slow deep IM deltoid injection for first 2 doses, then deep deltoid or gluteal injection (upper outer quadrant) thereafter</td>
<td>Occasional redness, swelling, induration</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Trinza</td>
<td>273/0.875 mL, 410/1.315 mL, 546/1.75 mL, 819/2.625 mL</td>
<td>Kit with Pre-filled syringe</td>
<td>IM only; Slow deep IM deltoid or gluteal injection</td>
<td>Infrequent redness or swelling</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal Consta</td>
<td>12.5, 25, 37.5, 50</td>
<td>Kit with pre-filled syringe and vial for reconstitution</td>
<td>Deep IM injection into the deltoid or gluteal (upper outer quadrant)</td>
<td>Occasional redness, swelling, induration</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Perseris</td>
<td>90, 120</td>
<td>Kit with pre-filled syringes containing powder and diluent.</td>
<td>Abdominal subcutaneous injection only</td>
<td>Lump at injection site may persist for several weeks</td>
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</table>

Table 8. Long-acting injectable antipsychotic medications: dosing\(^{24}\)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Dose conversions</th>
<th>Initial dose (mg)</th>
<th>Typical dose (mg)</th>
<th>Maximum dose (mg)</th>
<th>Dosing frequency</th>
<th>Need for initial oral supplementation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation Antipsychotics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolixin Decanoate</td>
<td>IM: PO ratio: 1:2.5</td>
<td>6.25 - 25 every 2 weeks</td>
<td>6.25 - 25 every 2-4 weeks</td>
<td>100</td>
<td>2 weeks</td>
<td>Decrease oral dose by half after first injection then discontinue with second injection</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol Decanoate</td>
<td>10-20 times the daily oral dose</td>
<td>Determined by oral dose and/or risk of relapse up to a maximum of 100 mg</td>
<td>50-200 (10-15 times previous oral dose)</td>
<td>450</td>
<td>4 weeks</td>
<td>Taper and discontinue after 2 to 3 injections</td>
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<td><strong>Second-Generation Antipsychotics</strong></td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify Maintena</td>
<td>Not applicable</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>Monthly</td>
<td>Continue oral for 14 days after initial injection</td>
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*IM: IM, PO: Oral*
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
<th>Dose conversions</th>
<th>Initial dose (mg)</th>
<th>Typical dose (mg)</th>
<th>Maximum dose (mg)</th>
<th>Dosing frequency</th>
<th>Need for initial oral supplementation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole lauroxil</td>
<td>Aristada</td>
<td>10 mg/day orally, give 441 mg IM/month 15 mg/day orally, give 662 mg/month IM, 882 mg IM every 6 weeks, or 1064 mg IM every 2 months 20 mg/day or greater orally, give 882 mg/month IM</td>
<td>Determined by oral dose</td>
<td>441-882/month, 882/6 weeks, 1064/2 months.</td>
<td>882/month</td>
<td>1-2 months</td>
<td>Use Aristada Initio 675 mg, first dose of Aristada based on oral dose with or within 10 days after the Aristada Initio dose, plus single 30 mg oral aripiprazole dose OR continue oral for 21 days after first Aristada injection</td>
<td>Aristada Initio syringes and doses are not interchangeable with other Aristada syringes and doses. See labeling for dose adjustments for concomitant therapy.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa Relprev</td>
<td>10 mg/day orally, 210 mg every 2 weeks for 4 doses or 405 mg every 4 weeks 15 mg/d orally, 300 mg every 2 weeks for 4 doses 20 mg/d orally, 300 mg every 2 weeks</td>
<td>Determined by oral dose</td>
<td>150 mg, 210 mg or 300 mg every 2 weeks, or 300 mg or 405 mg every 4 weeks</td>
<td>300 mg every 2 weeks or 405 mg every 4 weeks</td>
<td>2-4 weeks</td>
<td>Not required</td>
<td>Give 150 mg every 4 weeks in patients who may have sensitivity to side effects or slower metabolism. Smokers may require a greater daily dose than nonsmokers and women may need lower daily doses than expected.</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Dose conversions</td>
<td>Initial dose (mg)</td>
<td>Typical dose (mg)</td>
<td>Maximum dose (mg)</td>
<td>Dosing frequency</td>
<td>Need for initial oral supplementation</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
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<td>------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Sustenna 3 mg oral paliperidone give 39 to 78 mg IM 6 mg oral give 117 mg IM 9 mg oral give 156 mg IM 12 mg oral give 234 mg IM</td>
<td>234 mg IM on day 1 and 156 mg IM 1 week later</td>
<td>78 to 234 mg monthly beginning at week 5</td>
<td>234 mg</td>
<td>Monthly</td>
<td>Not required</td>
<td>Contains range of particle sizes for rapid and delayed absorption. For changes to oral or other LAI to Sustenna see labeling; doses are expressed as amount of paliperidone palmitate rather than as paliperidone. Avoid using with a strong inducer of CYP3A4 and/or P-glycoprotein.</td>
<td></td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Trinza Conversion from monthly Invega Sustenna to every 3-month injections of Invega Trinza. 78 mg give 273 mg 117 mg give 410 mg 156 mg give 546 mg 234 mg give 819</td>
<td>Dependent upon last dose of monthly paliperidone</td>
<td>273 - 819</td>
<td>819</td>
<td>Every 3 months</td>
<td>Not applicable</td>
<td>Change to Trinza after at least 4 Invega Sustenna doses (with 2 doses at same strength); for changes from IM Trinza to oral or to IM Sustenna, see labeling; doses are expressed as amount of paliperidone palmitate rather than as paliperidone. Avoid using with a strong inducer of CYP3A4 and/or P-glycoprotein.</td>
<td></td>
</tr>
<tr>
<td>Trade Name</td>
<td>Dose conversions</td>
<td>Initial dose (mg)</td>
<td>Typical dose (mg)</td>
<td>Maximum dose (mg)</td>
<td>Dosing frequency</td>
<td>Need for initial oral supplementation</td>
<td>Comments</td>
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<td>Risperidone</td>
<td>Risperdal Consta</td>
<td>Oral risperidone to Risperidone Consta IM:</td>
<td>25 every 2 weeks</td>
<td>25 - 50 every 2 weeks</td>
<td>50 every 2 weeks</td>
<td>2 weeks</td>
<td>Continue oral for 3 weeks (21 days)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤3 mg/d, give 25 mg/2 weeks</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>&gt; 3 to ≤ 5 mg/d, give 37.5 mg/2 weeks</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 5 mg/d, give 50 mg/2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Perseris</td>
<td>Oral risperidone to SubQ risperidone extended release:</td>
<td>Determined by oral dose</td>
<td>90 - 120 monthly</td>
<td>120 monthly</td>
<td>Monthly</td>
<td>Neither a loading dose nor oral overlap is needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg/d, give 90 mg/monthly</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>4 mg/day, give 120 mg/monthly</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Table 9. Long-acting injectable antipsychotic medications: pharmacological characteristics*\(^{25,26}\)

\(^{25}\) *Source.* Lexicomp 2019; Micromedex 2019; Procyshyn et al. 2019

\(^{26}\) *Source.* Package inserts references for long-acting injectable antipsychotic medication products: Jann et al. 1985; Lindenmayer 2010
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Time to peak plasma level</th>
<th>Time to steady state</th>
<th>Elimination half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Generation Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>8-10 hours</td>
<td>2 months</td>
<td>6-9 days for single injection and 14-26 days for multiple doses</td>
<td>Major CYP2D6 substrate</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6 days</td>
<td>2-4 months</td>
<td>21 days</td>
<td>Major CYP2D6 and CYP3A4 substrate</td>
</tr>
<tr>
<td><strong>Second-Generation Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>4 days (deltoid); 5 - 7 days (gluteal)</td>
<td>By 4&lt;sup&gt;th&lt;/sup&gt; dose</td>
<td>300 mg; 29.9 days, 400 mg; 46.5 days (400 mg) with gluteal injection</td>
<td>Give no sooner than 26 days between injections Major CYP2D6 and CYP3A4 substrate</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>Aristada Aristada Initio: 16 – 35 days (median 27 days); Aristada 4-6 days</td>
<td>4 months</td>
<td>Aristada Initio 15 to 18 days; Aristada 53.9 to 57.2 days</td>
<td>Major CYP2D6 and CYP3A4 substrate</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7 days</td>
<td>~3 months</td>
<td>30 days</td>
<td>Major CYP1A2 substrate</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>13 days</td>
<td>2-3 months</td>
<td>25 - 49 days; increased in renal disease</td>
<td>CrCl 50 – 79 mL/min: initiate at 156 mg on day 1, followed by 117 mg 1 week later. Maintenance dose of 78 mg; Use not recommended in patients with CrCl &lt; 50 mL/min Substrate of P-glycoprotein/ABCB1</td>
</tr>
</tbody>
</table>

<sup>27</sup> If a dose of a long-acting injectable antipsychotic medication is missed, refer to product labeling for information on adjustments to medication dose or administration frequency.
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Trade Name</th>
<th>Time to peak plasma level</th>
<th>Time to steady state</th>
<th>Elimination half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Trinza</td>
<td>30 - 33 days</td>
<td>Not applicable</td>
<td>84 - 95 days with deltoid injection; 118 - 139 days with gluteal injection; increased in renal disease</td>
<td>Do not use in patients with CrCl &lt;50 mL/min. Substrate of P-glycoprotein/ABCB1</td>
</tr>
<tr>
<td>Risperidone Risperdal</td>
<td>Constra</td>
<td>29 - 31 days</td>
<td>2 months</td>
<td>3 - 6 days; increased in renal or hepatic disease</td>
<td>For renal/hepatic impairment: Initiate with oral dosing (0.5 mg twice a day for 1 week then 1 mg twice a day or 2 mg daily for 1 week); if tolerated, begin 25 mg IM every 2 weeks; continue oral dosing for 21 days. An initial IM dose of 12.5 mg may also be considered Major substrate of CYP2D6 and minor substrate of CYP3A4 (minor) substrate; weak CYP2D6 inhibitor</td>
</tr>
<tr>
<td>Risperidone Perseris</td>
<td></td>
<td>Two peaks: 4 - 6 hours and 10 - 14 days</td>
<td>2 months</td>
<td>9 - 11 days</td>
<td>For renal/hepatic impairment: Use with caution with renal impairment; has not been studied. If oral risperidone is tolerated and effective at doses up to 3 mg/day, 90 mg/month can be considered. Major CYP2D6 substrate and minor CYP3A4 substrate; weak CYP2D6 inhibitor</td>
</tr>
</tbody>
</table>
Factors Influencing Choice of an Antipsychotic Medication

Available Drug Formulations
Medication choice may be influenced by available formulations of specific medications such as oral concentrates or rapid dissolving tablets for patients who have difficulty swallowing pills or who are ambivalent about medications and inconsistent in swallowing them. Use of ingestible sensors with associated monitoring technology may assist in evaluating adherence, although the U.S. Food and Drug Administration (FDA) notes that improvements in adherence have not yet been shown (Food and Drug Administration 2017). LAI formulations may be preferred by some patients (Heres et al. 2007; Patel et al. 2009; Walburn et al. 2001) and, although evidence is mixed (Kirson et al. 2013; Kishi et al. 2016a, 2016b; Kishimoto et al. 2018; Lafeuille et al. 2014; MacEwan et al. 2016b; Misawa et al. 2016; Ostuzzi et al. 2017; Taipale et al. 2018; Tiihonen et al. 2017), they may be particularly useful for patients with frequent relapses related to nonadherence. Short-acting parenteral formulations of antipsychotic agents are available for short-term use in individuals who are unable to take oral medications or for emergency administration in acutely agitated patients.

Drug-drug Interactions and Metabolism
Careful attention must be paid to the potential for interactions of antipsychotic agents with other prescribed medications. For example, when multiple medications are prescribed, side effects (e.g., sedation, anticholinergic effects) can be additive. In addition, drug interactions can influence the amount of free drug in the blood that is available to act at receptors. Because most antipsychotic medications are highly bound to plasma proteins, the addition of other protein bound medications will displace drug molecules from proteins, resulting in a greater proportion of unbound drug in the blood. Another common cause of drug-drug interactions relates to the fact that many antipsychotic medications are metabolized in the liver via cytochrome P450 (CYP) enzymes. Medications may compete with each other for the same CYP enzyme or they may induce or inhibit the activity of CYP enzymes, altering levels of drugs that are metabolized through that route. For antipsychotic medications that have active metabolites, shifts in CYP enzyme activity can influence the relative amounts of the active metabolite. Consequently, when a patient is taking multiple medications, it is useful to check for possible drug-drug interactions using electronic drug interaction software (e.g., web-based software, drug interaction checking embedded in electronic health record software).

In addition to drug-drug interactions, a number of other factors can influence CYP enzymes and thereby affect antipsychotic medication levels in blood. For example, smoking tobacco or marijuana induces CYP1A2 resulting in a corresponding reduction of levels of drugs that are metabolized through that enzyme including clozapine and olanzapine (Anderson and Chan 2016; Kroon 2007; Scherf-Clavel et al. 2019). Conversely, with cessation of smoking (either intentionally or with admission to a smoke-free facility), there will be corresponding increases in the levels of drugs metabolized via CYP1A2. These shifts in blood levels can be quite significant and contribute to shifts in medication effectiveness or toxicity. Several of the main phytocannabinoids in marijuana (e.g., Δ9-tetrahydrocannabinol, cannabidiol) are metabolized via CYP3A4 and cannabidiol may also inhibit CYP2C19 (Anderson and Chan 2016).
Furthermore, levels of antipsychotic medications, the relative proportions of active metabolites, and other pharmacokinetic properties such as medication or active metabolite half-life can be influenced by genetic differences in metabolic enzyme activity. Polymorphisms of CYP2D6 have been subjected to the most study (Brennan 2014; Zhou 2009), show substantial variation in their occurrence in the population by ethnicity (Bertilsson 2007; Gaedigk et al. 2017), and are likely to have the greatest potential for impact on antipsychotic medication metabolism. Polymorphisms of the ATP-binding cassette subfamily B member 1 (ABCB1) gene, which affects P-glycoprotein membrane transport, may influence brain concentrations of drugs, including antipsychotic agents (Moons et al. 2011). Although the applicability of gene polymorphism testing to the clinical choice of an antipsychotic medication is still being explored (Koopmans et al. 2018; Lagishetty et al. 2016; Macaluso and Preskorn 2018), the FDA has incorporated testing for CYP2D6 polymorphisms into its labeling recommendations for dosing of pimozide based on the increased risk of electrocardiographic changes in poor metabolizers at doses higher than 4 mg/d (0.05 mg/kg/d in children) (Food and Drug Administration 2011).

**Pharmacokinetic Properties**

The absorption of some antipsychotic medications is affected by the presence of food in the stomach. (See Tables 3 and 4.) Some individuals may have difficulty in adhering to appropriate meal size or content, which could influence choice of these medications.

The half-life of an antipsychotic medication is another pharmacokinetic property that may be useful to consider in choosing among antipsychotic agents. Antipsychotic agents with a short half-life (see Tables 3 and 4) are more likely to require divided dosing in contrast to antipsychotic medications with a half-life that is closer to 24 hours. An oral antipsychotic medication with a longer half-life may be preferable for patients who are prone to forget doses or who are intermittently nonadherent to treatment. Nevertheless, if an antipsychotic medication (or active metabolite) half-life is significantly longer than 24 hours, it is important to be aware that steady state may not be reached for some time. This can complicate interpreting the patient's response to adjustments in doses in terms of therapeutic benefits and side effects. Additional caution may be needed when an antipsychotic medication with a long half-life is chosen for older individuals, for an individual who is taking other medications that may affect drug metabolism, or for individuals with renal or hepatic impairment.

Older individuals often exhibit additional physiological changes relative to younger persons including a reduced cardiac output (and concomitant reduction in renal and hepatic blood flow), reduced glomerular filtration rate, possible reduction in hepatic metabolism, and increased fat content. These changes may alter the absorption, distribution, metabolism, and excretion of medications and may also result in prolonged drug effects and greater sensitivity to medications, in terms of both therapeutic response and side effects (Kaiser 2015).

**Side Effect Profile**

The side effect profile of an antipsychotic agent is a significant factor in the choice of a specific medication. (See Table 6.) Often a patient will express concerns about a particular side effect of medication (e.g., weight gain), or a specific side effect (e.g., akathisia, weight gain, sedation, or sexual dysfunction) may have limited treatment adherence in the past. If a patient has a concomitant physical
condition (e.g., diabetes, cardiac conduction abnormalities, or a seizure disorder), this may also lead to a choice of medication that would be less likely to exacerbate an existing health condition. Older individuals may be more sensitive to some medication side effects such as tardive dyskinesia, orthostatic hypotension, or anticholinergic effects of medications. Thus, a medication might be preferred that has a lower likelihood of these side effects. In contrast, there may be circumstances in which a medication side effect may be helpful. For example, in a patient who is not sleeping well, a more sedating antipsychotic might be chosen and administered at bedtime. Regardless of the initial side effect-related considerations in the choice of an antipsychotic medication, it is important to continue to monitor for side effects as treatment proceeds and to have additional discussions with the patient about side effects as they relate to treatment preferences.

Initiation of Treatment With an Antipsychotic Medication

The initial goal of acute treatment with an antipsychotic medication is to reduce acute symptoms with the aim of returning the individual to their baseline level of functioning. Later, maintenance treatment will aim to prevent recurrence of symptoms and maximize functioning and quality of life.

The initial dose of medication will depend on factors such as the medication formulation, the characteristics of the patient, and whether a prior trial of antipsychotic medication has occurred. With the exception of clozapine, the dose of most antipsychotic medications can be increased relatively quickly to a typical therapeutic dose, once an initial dose has been tolerated. For patients who have previously been treated with an oral or LAI antipsychotic medication, more rapid resumption of an effective medication dose is often appropriate. However, with patients who are experiencing a first episode of psychosis, some clinicians feel that a lower initial medication dose may help in minimizing acute side effects of antipsychotic medication and improve patient's willingness to continue with treatment. In older individuals, particularly those with concomitant physical health issues who are receiving multiple medications, recommended starting doses of medication are one-quarter to one-half of the usual adult starting dose (Howard et al. 2000). If treatment is planned with a LAI antipsychotic medication, a longer trial of oral medication is usually given to determine the likely dose of LAI antipsychotic that will be needed and to assure tolerability.

Determining the optimal dose of antipsychotic medication during acute treatment is complicated by the fact that there is usually a delay between initiation of treatment and full therapeutic response. Patients may take between two and four weeks to show an initial response and up to six months or longer to show full or optimal response. Once a therapeutic dose of the antipsychotic medication is reached, overly rapid or premature escalation of medication doses can affect tolerability. Premature dose increases can also create the false impression of enhanced efficacy due to a higher dose when the observed response is actually related to elapsed time at a steady state level of medication. Consequently, monitoring of the patient's clinical status for two–four weeks is warranted on a therapeutic dose unless the patient is having uncomfortable side effects. Although as needed or emergency administration of antipsychotic medication may, at times, be useful in individuals with acute agitation, they can also reduce tolerability and contribute to a perception that premature dose increases are needed.
Initiation of treatment with clozapine is a notable exception to this general approach as it requires a slow dose titration to minimize the risks of seizure, orthostatic hypotension, and excessive sedation (HLS Therapeutics 2017). Large, rapid increases in clozapine dosage have led to cardiovascular collapse and death, particularly in patients taking respiratory depressant medications such as benzodiazepines. From a starting dose of 12.5 mg once or twice daily, the daily clozapine dose can be increased by, at most, 25 mg to 50 mg per day to a target dose of 300 mg to 450 mg per day, in divided doses (HLS Therapeutics 2017). Subsequent dose increases, if needed, should be of 100 mg or less, once or twice weekly.

Although efficacy is often seen at a dose of 300 to 450 mg per day, some individuals may need higher dosages of clozapine, to a maximum daily dose of 900 mg, for full response.

With clozapine, safety monitoring during treatment is important to minimize the risk of adverse events. The U.S. Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (www.clozapinerems.com)\(^\text{28}\) includes required training that must be completed by prescribers (Clozapine REMS 2019a), resource materials (Clozapine REMS 2019b), and a shared patient registry for all clozapine manufacturers’ products that permits tracking of absolute neutrophil counts (ANCs) and documentation of decisions about continued treatment. The Clozapine REMS site provides instructions about threshold values for ANCs in hematologically-normal individuals and in those with benign ethnic neutropenia, which is most common in individuals of African descent and associated with normal ANCs that are lower than standard reference ranges (Clozapine REMS 2014). It also describes the required frequencies for ANC monitoring, which vary with ANC values. Because the highest risk of severe neutropenia (ANC <500) occurs in the initial month of clozapine treatment (Myles et al. 2018), the frequency of ANC monitoring is also reduced with longer treatment duration. In patients who have stopped or interrupted treatment with clozapine for 30 days or more, the monitoring frequency for treatment initiation will be needed.

With clozapine as well as with other antipsychotic medications, some common early side effects such as sedation, postural hypotension, or nausea may improve or resolve after the first several days or weeks of treatment, and patients can be encouraged to tolerate or temporarily manage these short-term effects. Other side effects, notably akathisia and parkinsonism, are likely to persist with long-term treatment and additional approaches to management may be needed. (See Guideline Statements 11 and 12).

**Strategies to Address Initial Non-response to Antipsychotic Treatment**

If no factors have been identified that would affect treatment response and if there is no significant improvement after several weeks of treatment, raising the dose for a finite period, such as two–four weeks, can be tried. Although the incremental efficacy of higher doses has not been well established, some patients may show benefit if able to tolerate a higher dose of antipsychotic medication without significant side effects. If dose adjustment does not result in an adequate response, a different antipsychotic medication should be considered. Because each patient responds differently to antipsychotic medications in terms of therapeutic effects and side effects, adequate trials of multiple antipsychotic medications may be needed before antipsychotic treatment is optimized. A clozapine trial

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\(^{28}\) For Canadian prescribers, use the appropriate Canadian clozapine registry and not the U.S. Clozapine REMS program.
should be considered for a patient with persistent risk of suicide or aggressive behavior that has not responded to other treatments, as well as for a patient who has had minimal or no response to two trials of antipsychotic medication of at least six weeks duration at an adequate dose (Howes et al. 2017). (See Guideline Statements 5, 6, and 7.) Some individuals may show a response to treatment (i.e., have more than a 20% reduction in symptoms) yet still have significant symptoms or impairments in functioning (Howes et al. 2017). A trial of clozapine may also be appropriate under these circumstances.

Monitoring During Treatment With an Antipsychotic Medication

During treatment with an antipsychotic medication, it is important to monitor medication adherence, therapeutic benefits of treatment, and treatment-related side effects. The patient's clinical status can also be affected by changes in physical health, adjustments to other psychotropic and non-psychotropic medications, and other factors, such as cessation or resumption of smoking.

Adherence with antipsychotic treatment is a common problem that affects treatment outcomes. There are many barriers to treatment adherence as well as facilitators and motivators of adherence, each of which will differ for an individual patient (Hatch et al. 2017; Kane et al. 2013; Pyne et al. 2014). Thus, it is important to take a patient-centered approach in inquiring in a non-judgmental way whether the individual has experienced difficulties with taking medication since the last visit. Issues that may influence adherence include, but are not limited to, forgetting to take doses, difficulties managing complex regimens (e.g., due to cognitive impairment, frequency of doses, or number of medications), side effects that are of particular importance to the patient (e.g., weight gain, akathisia, sexual dysfunction), financial barriers (e.g., cost, insurance coverage), insufficient understanding of medication benefits for symptoms that are important to the patient, high levels of hostility, persecutory delusions, suspiciousness of medications or treatment in general, lack of a perceived need for treatment (e.g., due to feeling good or not viewing self as ill, due to personal, religious, or cultural beliefs), co-occurring conditions (e.g., depression, alcohol, cannabis, or other substance use disorder), prior difficulties with adherence, prior experiences with treatment (e.g., effectiveness, side effects), difficulties in the therapeutic relationship, lack of support from significant others for treatment, or perceptions of stigma about having an illness or taking medication (Acosta et al. 2012; Ascher-Svanum et al. 2006; Czobor et al. 2015; Foglia et al. 2017; García et al. 2016; Haddad et al. 2014; Hartung et al. 2017; Hatch et al. 2017; Higashi et al. 2013; Kane et al. 2013; MacEwan et al. 2016a; Pyne et al. 2014; Shafrin et al. 2016; Velligan et al. 2017; Volavka et al. 2016; Wade et al. 2017). Adherence with appointments can also be influenced by financial barriers, scheduling difficulties, or issues with transportation or with childcare.

Monitoring of treatment response is also essential to identify whether target symptoms or functional impairments are being reduced or whether additional assessment is needed to determine reasons for a lack of response. If an antipsychotic medication dose is being decreased, monitoring can help detect a return of symptoms prior to a more serious relapse. Use of a quantitative measure (see Guideline Statement 2) can assist in evaluating symptom severity and can detect whether the antipsychotic medication is producing therapeutic benefits. Although full response can take weeks to months, an absence of benefit after several weeks may be due to factors such as reduced medication adherence, concomitant substance use, rapid medication metabolism, poor medication absorption, or interactions with other medications that are affecting blood levels of the drug. Determination of the blood
concentration of the drug may be helpful if the patient is being treated with a medication (e.g., clozapine) for which blood level has some correlation with clinical response. Depending on the patient's symptoms, the possibility of another concomitant disorder should be considered. For example, in a patient with negative symptoms, an untreated major depressive disorder may also be present.

Monitoring for the presence of side effects is also important throughout the course of antipsychotic treatment. Some side effects are prominent with treatment initiation but dissipate, at least to some extent, with continued treatment. Other side effects may be present initially but increase in severity with titration of the medication dose (e.g., hypotension, akathisia) or become more noticeable to patients as their acute symptoms are better controlled (e.g., sexual dysfunction). Still other side effects, such as tardive dyskinesia, emerge only after longer periods of treatment. Table 2 in Guideline Statement 1 gives suggestions for baseline assessments and monitoring frequencies for some side effects, clinical measurements, and laboratory studies. Patients should also be asked about other common side effects of antipsychotic medications, which may vary with the specific medication that is prescribed. (See Table 6.)

Use of rating scales can help assure that patients are asked about side effects in a systematic fashion. Although the clinician-rated UKU Side Effect Rating Scale (Lingjaerde et al. 1987) is often used to assess side effects of antipsychotic medications in clinical trials (van Strien et al. 2015), it can be time-consuming to administer. However, a self-rated version of the UKU Side Effect Rating Scale is also available (Lindström et al. 2001). Another self-rating scale, the Glasgow Antipsychotic Side Effect Scale (GASS) has two versions: one for use in patients treated with clozapine (Hynes et al. 2015) and one for patients treated with other antipsychotic medications (Waddell and Taylor 2008). Other rating scales are aimed at identifying and assessing the severity of a specific type of side effect. For example, the clinician-administered Abnormal Involuntary Movement Scale can be used to identify and monitor tardive dyskinesia and other abnormal movements (Guy 1976). Another example, the self-rated Changes in Sexual Functioning Questionnaire (Clayton et al. 1997a, 1997b; Depression and Bipolar Support Alliance 2019; Keller et al. 2006), can help to identify sexual side effects of antipsychotic treatment, which is an issue that patients may find difficult to discuss yet can lead them to discontinue treatment.

Treatment-emergent Side Effects of Antipsychotic Medications
As with most medications, antipsychotic medications have been associated with a number of side effects that can develop as treatment proceeds. Table 6 shows the relative tendencies for antipsychotic medications to be associated with specific side effects. In addition, each of these side effects is described in further detail below.

Early in the course of treatment, common side effects include sedation, orthostatic changes in blood pressure, and anticholinergic side effects such as dry mouth, constipation, and difficulty with urination. Prolongation of QTc intervals can also be a concern early in treatment because of the potential for life-threatening torsades de pointes (TdP).

Of the side effects related to dopamine D2 receptor antagonist effects of antipsychotics, acute dystonia also appears early in treatment. It is particularly common with high-potency antipsychotic medications.
(e.g., haloperidol, fluphenazine) and can be life-threatening if associated with laryngospasm. Neuroleptic malignant syndrome (NMS) typically occurs within the first month of antipsychotic treatment (or resumption of treatment) and can also be life-threatening because of associated hyperthermia and autonomic instability. Akathisia and neuroleptic-induced parkinsonism can also occur in the initial weeks of treatment or after increases in medication doses. Hyperprolactinemia, related to D2 receptor antagonism in the hypothalamic-pituitary axis, can lead to breast enlargement, galactorrhea, sexual dysfunction, and, in women, menstrual disturbances. These elevations in prolactin also occurs in the initial weeks to months of treatment. On the other hand, tardive syndromes including tardive dyskinesia develop later, often months or even years after treatment initiation.

Side effects related to metabolic syndrome are common and generally observed in the initial months of treatment but can also occur later in treatment. These include weight gain, hyperlipidemia, and glucose dysregulation including development of diabetes mellitus.

Clozapine treatment is associated with a number of side effects that are less commonly seen with other antipsychotic medications. Severe neutropenia is most often seen early in treatment and is potentially life-threatening. However, it is rare, with current regulatory requirements for monitoring ANC levels during treatment. When seizures occur with clozapine, it is typically with very high doses of clozapine, rapid increases in clozapine dose, or shifts in medication levels (related to drug-drug interactions or effects of smoking on drug metabolism). Myocarditis is infrequent and generally occurs early in treatment. Cardiomyopathy is rare and generally occurs later in the treatment course. Gastrointestinal effects of clozapine can also be significant and in some patients associated with fecal impaction or paralytic ileus. Sialorrhea and tachycardia are each commonly observed during treatment with clozapine but are generally able to be managed conservatively.

Allergic and Dermatological Side Effects
Cutaneous allergic reactions occur infrequently with antipsychotic medications, but hypersensitivity can manifest as maculopapular erythematous rashes typically of the trunk, face, neck, and extremities. Medication discontinuation or administration of an antihistamine is usually effective in reversing these symptoms.

In terms of other dermatological side effects, thioridazine treatment is rarely noted to be associated with hyperpigmentation of the skin. Photosensitivity reactions, resulting in severe sunburn, are also most commonly observed with low-potency phenothiazine medications. A blue-gray discoloration of the skin has been reported in patients receiving long-term chlorpromazine treatment in body areas exposed to sunlight. Consequently, patients who are taking these medications should be instructed to avoid excessive sunlight and use sunscreen.

Cardiovascular Effects
Hyperlipidemia
There is some evidence that certain antipsychotic medications, particularly clozapine and olanzapine, may increase the risk for hyperlipidemias (Buhagiar and Jabbar 2019; Bushe and Paton 2005; Meyer and Koro 2004; Mitchell et al. 2013a). However, there is also a suggestion that some patients may have a
dyslipidemia prior to starting on antipsychotic treatment (Misiak et al. 2017; Pillinger et al. 2017b; Yan et al. 2013). Some patients develop an elevation of triglyceride levels in association with antipsychotic treatment that rarely is sufficiently high as to be associated with development of pancreatitis (Alastal et al. 2016). It is unclear whether triglyceridemia with antipsychotic treatment is a direct result of the medication or an indirect result of increased triglycerides in the blood with concomitant diabetes (Yan et al. 2013). In any patient with hyperlipidemia, it is also important to assess for other contributors to metabolic syndrome (Mitchell et al. 2013b; Mitchell et al. 2012) and ensure that the patient is receiving treatment with a lipid-lowering agent, as clinically indicated.

Myocarditis and Cardiomyopathy

Myocarditis and cardiomyopathy are rare side effects that have been reported in patients treated with clozapine and have resulted in death in some individuals. The etiology of these cardiac effects is unclear although an immune-mediated mechanism has been suggested (Røge et al. 2012). For myocarditis, the reported incidence has varied from 0.015% to 8.5% (Bellissima et al. 2018). For reasons that are unclear, the highest rates have been reported in Australia (Ronaldson et al. 2015); rates elsewhere appear to be much lower. For example, an early study using the U.S. Clozaril National Registry found 17 confirmed cases of myocarditis in a total of 189,405 individuals who had received clozapine (La Grenade et al. 2001). A recent national registry study of outpatients in Denmark found 1 of 3,262 (0.03%) clozapine-treated patients developed myocarditis in the initial 2 months of treatment (Rohde et al. 2018). These authors estimated that a maximum of 0.28% of patients treated with clozapine would experience fatality due to clozapine-associated myocarditis, which is comparable to rates of cardiac adverse effects with other antipsychotic medications. For cardiomyopathy the reported incidence is even less clear but appears to be considerably lower than rates of clozapine-associated myocarditis (Higgins et al. 2019; Khan et al. 2017; Rohde et al. 2018; Ronaldson et al. 2015).

Although cardiomyopathy has been reported throughout the course of clozapine treatment, the onset of myocarditis is typically during the first month of treatment and heralded by shortness of breath, tachycardia, and fever (Bellissima et al. 2018; Ronaldson et al. 2015). Other features can include fatigue, chest pain, palpitations, and peripheral edema. Diagnosis can be challenging due to the non-specific nature of these symptoms. For example, primary tachycardia is common with clozapine treatment without signifying underlying cardiac disease. Fever can also occur with clozapine initiation, yet often resolve quickly and without evidence of myocarditis (Bruno et al. 2015; Lowe et al. 2007; Pui-yin Chung et al. 2008).

Recommendations for monitoring have varied but there is no evidence or consensus that preemptive screening is necessary or helpful. However, if myocarditis or cardiomyopathy is suspected, a recent systematic review suggests seeking cardiology consultation as well as monitoring C-reactive protein, troponin (I and T subtypes), and obtaining electrocardiography as indicated (Knoph et al. 2018). Cardiac magnetic resonance imaging may also be indicated in some individuals.

In patients who do develop myocarditis or cardiomyopathy in conjunction with clozapine treatment, clozapine is typically discontinued. Subsequent decisions about resuming clozapine are individualized and based on the benefits and risks of treatment as compared to other therapeutic alternatives.
Orthostatic Hypotension

Orthostatic hypotension, a drop-in blood pressure when changing from lying or sitting to standing, is dose-related and due to the alpha-receptor blocking effects of antipsychotic medications. When severe, orthostatic hypotension can cause syncope, dizziness, or falls. Older or severely debilitated patients, patients in the dose-titration phase of clozapine therapy, and patients with peripheral vascular disease or a compromised cardiovascular status may be at particular risk. Patients who experience orthostatic hypotension must be cautioned to sit on the edge of the bed for a minute before standing up, move slowly when going from lying or sitting to standing and to seek assistance when needed. Management strategies for orthostatic hypotension include using supportive measures (e.g., use of support stockings, increased dietary salt and fluid intake), reducing the speed of antipsychotic dose titration, decreasing or dividing doses of antipsychotic medication, switching to an antipsychotic medication without antiadrenergic effects, and, as a last resort, administration of the salt/fluid retaining corticosteroid, fludrocortisone, to increase intravascular volume (Mar and Raj 2018; Shen et al. 2017). For patients who are receiving concomitant antihypertensive treatment, adjustments to the dose of these medications may be needed.

QTc Prolongation

The QT interval on the electrocardiogram reflects the length of time required for ventricular repolarization and varies with heart rate (Funk et al. 2018). Several approaches exist for calculating a QT interval corrected for heart rate (“QTc”) although each approach has limitations. Significant prolongation of the QTc interval is associated with increased risk for a ventricular tachyarrhythmia, “TdP”, which can lead to life-threatening consequences (e.g., ventricular fibrillation, sudden death). When the QTc interval is prolonged, a decision about the antipsychotic medication choice or changes requires a comprehensive risk-benefit assessment. A QTc interval > 500 msec is sometimes viewed as a threshold for concern; however, "there is no absolute QTc interval at which a psychotropic should not be used" (Funk et al. 2018).

Studies that have examined the risks of QTc prolongation with antipsychotic treatment have varied in study quality, sample sizes, and the physical health of study subjects. Sources are available that categorize medications based on their level of risk for QTc prolongation and TdP (Woosley 2009), but the quality of data that informs such categorizations is also variable (Funk et al. 2018). Nevertheless, among the FGAs, chlorpromazine, thioridazine, pimozide, and haloperidol appear to be associated with the greatest risk of QTc prolongation. The FDA recommends that thioridazine should be used only when patients have not had a clinically acceptable response to other available antipsychotics (National Institutes of Health 2018b). Pimozide labelling also includes specific instructions related to medication dosing and QTc interval prolongation (National Institutes of Health 2018a). Orally-administered haloperidol has only been associated with a mild increase in QTc interval length in healthy individuals; however, the risk of QTc interval prolongation and TdP appears to be greater in medically ill individuals with intravenous administration (Funk et al. 2018). Most SGAs have also been associated with some QTc interval prolongation, with ziprasidone, quetiapine, and iloperidone appearing to have the greatest likelihood of QTc prolongation. The FDA has required that a warning about QTc prolongation be included
with product labeling for ziprasidone (Pfizer 2018) and for quetiapine (Anonymous 2011; AstraZeneca
2018).

Factors to consider when making a determination about selecting or changing antipsychotic medications include whether the patient is taking other medications that are known to prolong QTc intervals; whether the patient has factors that would influence drug metabolism leading to higher blood levels of drug (e.g., poor metabolizer status, pharmacokinetic drug-drug interactions, hepatic or renal disease, drug toxicity); whether the patient is known to have a significant cardiac risk factor (e.g., congenital long QT syndrome, structural or functional cardiac disease, bradycardia, family history of sudden cardiac death); or other factors associated with an increased risk of TdP (e.g., female sex, advanced age, personal history of drug-induced QTc prolongation, severe acute illness, starvation, or risk or presence of hypokalemia, hypomagnesemia or hypocalcemia) (Funk et al. 2018). For individuals with these risk factors, antipsychotic medications with regulatory warning or those with a known risk of QTc prolongation are not recommended for use if safer medication alternatives are available. Input from cardiology consultants should be considered when significant cardiac disease or other risk factors for QTc prolongation is present, although routine cardiology consultation is not indicated for patients without cardiac risk factors (Funk et al. 2018).

Tachycardia

Tachycardia can be primary (e.g., with clozapine), a reflex response to orthostatic hypotension, or a result of anticholinergic effects. It appears to be particularly common in individuals who are treated with clozapine (Lally et al. 2016a), but may also be seen in individuals treated with other antipsychotic medications, particularly low-potency phenothiazines. Although healthy patients may be able to tolerate some increase in resting pulse rate, this may not be the case for patients with preexisting heart disease. In patients with significant tachycardia (heart rates above 110 to 120 bpm), an Electrocardiography (ECG) is warranted as is an assessment for other potential causes of tachycardia (e.g., fever, anemia, smoking, hyperthyroidism, respiratory disease, cardiovascular disorders, caffeine and other stimulants, and side effects of other medications). Early in treatment with clozapine, the possibility of myocarditis should be considered. Management strategies for tachycardia with antipsychotic medications include reducing the dose of medication, discontinuing medications with anticholinergic or stimulant properties, and using the strategies described above to reduce any contributing orthostatic hypotension. Case reports have discussed the use of medications such as beta-blocking agents for persistent and significant tachycardia with clozapine, but data from more rigorous studies is not available and these medications can contribute to other side effects such as orthostatic hypotension (Lally et al. 2016a). If tachycardia is accompanied by pain, shortness of breath, fever, or signs of a myocardial infarction or heart rhythm problem, emergency assessment is essential.

Endocrine Side Effects

Glucose Dysregulation and Diabetes Mellitus

Evidence from meta-analyses of randomized controlled trials, population-based studies, and case-control studies suggests that some antipsychotic medications, clozapine and olanzapine in particular, are associated with an increased risk of hyperglycemia and diabetes (Hirsch et al. 2017; Ward and Druss...
Complicating the evaluation of antipsychotic-related risk of diabetes is that some patients with first-episode psychosis seem to have abnormal glucose regulation that precedes antipsychotic treatment (Greenhalgh et al. 2017; Perry et al. 2016; Pillinger et al. 2017a). In addition, obesity and treatment-related weight gain may contribute to diabetes risk. Nevertheless, there are some patients without other known risk factors who develop insulin resistance early in the course of antipsychotic treatment. In some individuals, diabetic ketoacidosis and nonketotic hyperosmolar coma have been reported in the absence of a known diagnosis of diabetes (Guenette et al. 2013; Kato et al. 2015; Liao and Phan 2014; Polciwiartek et al. 2016; Vuk et al. 2017). Given the rare occurrence of extreme hyperglycemia, ketoacidosis, hyperosmolar coma, or death and the suggestion from epidemiological studies of an increased risk of treatment-emergent adverse events with SGAs, the FDA has requested all manufacturers of SGA medications to include a warning in their product labeling regarding hyperglycemia and diabetes mellitus (American Society of Health-System Pharmacists 2004). When individuals with schizophrenia do develop diabetes, management principles should follow current guidelines for any patient with diabetes (Holt and Mitchell 2015; Scott et al. 2012). The clinician can also help in ensuring that patients are obtaining appropriate diabetes care, given frequent health disparities for individuals with serious mental illness (Mangurian et al. 2016; Scott et al. 2012), and encourage patients to engage in lifestyle interventions to improve diabetes self-management (Cimo et al. 2012). In any patient with diabetes, it is also important to assess for other contributors to metabolic syndrome (Mitchell et al. 2012; Mitchell et al. 2013b).

Hyperprolactinemia

Prolactin elevation is frequent in patients treated with antipsychotics (Ajmal et al. 2014; Cookson et al. 2012; Kinon et al. 2003; Lally et al. 2017a; Leucht et al. 2013; Rubio-Abadal et al. 2016), which increase prolactin secretion by blocking the inhibitory actions of dopamine on lactotrophic cells in the anterior pituitary. Consequently, hyperprolactinemia is observed more frequently with the use of antipsychotics that are more potent at blocking dopamine receptors (Tsuboi et al. 2013).

In both men and women, prolactin-related disruption of the hypothalamic-pituitary-gonadal axis can lead to decreased sexual interest and impaired sexual function (Kirino 2017; Rubio-Abadal et al. 2016). Other effects of hyperprolactinemia may include breast tenderness, breast enlargement, and lactation (Ajmal et al. 2014; Cookson et al. 2012). Because prolactin also regulates gonadal function, hyperprolactinemia can lead to decreased production of gonadal hormones, including estrogen and testosterone, resulting in disruption or elimination of menstrual cycles in women. In addition, in lactating mothers, suppression of prolactin may be detrimental, and the potential for this effect should be considered.

The long-term clinical consequences of chronic elevation of prolactin are poorly understood. Chronic hypogonadal states may increase the risk of osteopenia/osteoporosis and fractures may be increased in individuals with schizophrenia, but a direct linked to antipsychotic-induced hyperprolactinemia has not been established (Bolton et al. 2017; Stubbs et al. 2014; Stubbs et al. 2015; Tseng et al. 2015; Weaver et al. 2019). In addition, some concern has been expressed about potential effects of hyperprolactinemia on the risk of breast or endometrial cancer; however, the available evidence suggests that such risks, if
they exist, are likely to be small (De Hert et al. 2016; Froes Brandao et al. 2016; Klil-Drori et al. 2017; Pottegård et al. 2018; Wang et al. 2002).

If a patient is experiencing clinical symptoms of prolactin elevation, the dose of antipsychotic may be reduced or the medication regimen may be switched to an antipsychotic with less effect on prolactin such as an antipsychotic with partial agonist activity at dopamine receptors (Ajmal et al. 2014; Grigg et al. 2017; Yoon et al. 2016). Administration of a dopamine agonist such as bromocriptine may also be considered.

**Sexual Function Disturbances**

A majority of patients with schizophrenia report some difficulties with sexual function. Although multiple factors are likely to contribute and rates vary widely depending on the study, it is clear that antipsychotic treatment contributes to sexual dysfunction (de Boer et al. 2015; La Torre et al. 2013; Marques et al. 2012; Serretti and Chiesa 2011; van Dijk et al. 2018). Effects of antipsychotic agents on sexual function may be mediated directly via drug actions on adrenergic and serotonergic receptors or indirectly through effects on prolactin and gonadal hormones (Kirino 2017; Knegtering et al. 2008; Rubio-Abadal et al. 2016). Loss of libido and anorgasmia can occur in men and in women; erectile dysfunction and ejaculatory disturbances also occur in men (La Torre et al. 2013; Marques et al. 2012; Serretti and Chiesa 2011; van Dijk et al. 2018). Retrograde ejaculation has also been reported with specific antipsychotic medications (e.g., thioridazine, risperidone) (Chouinard et al. 1993; de Boer et al. 2015; Kotin et al. 1976). In addition, it is important to note that priapism can also occur in association with antipsychotic treatment, particularly in individuals with other underlying risk factors such as sickle cell disease (Burnett and Bivalacqua 2011; Sood et al. 2008).

Despite the high rates of occurrence of sexual dysfunction with antipsychotic medication, many patients will not spontaneously report such difficulties. Thus, it is important to ask patients specifically about these side effects. Structured rating scales also exist to assess sexual side effects during antipsychotic treatment, and these can be used to supplement information obtained via interview (Clayton et al. 1997a, 1997b; de Boer et al. 2014; Depression and Bipolar Support Alliance 2019; Keller et al. 2006). Education about sexual side effects of medication can also be provided to the patient to communicate that these symptoms may occur but can be addressed (de Boer et al. 2015).

When sexual side effects of antipsychotic therapy are of significant concern to the patient, a reduction in medication dose or change in medication may be considered in addition to an assessment of other potential contributing factors (e.g., hyperprolactinemia, other medications, psychological factors) (de Boer et al. 2015; La Torre et al. 2013). Priapism, if it occurs, requires urgent urological consultation.

**Gastrointestinal Side Effects**

The most common gastrointestinal side effects of antipsychotic medications are related to anticholinergic side effects and include dry mouth and constipation as noted above. Patients and families should be educated about constipation and, if present, constipation should be reported promptly to clinicians. In some instances, with clozapine in particular, gastrointestinal hypomotility can
be severe and can result in fecal impaction or paralytic ileus (Every-Palmer and Ellis 2017; Leung et al. 2017). Thus, if constipation is severe or does not resolve, the patient should obtain urgent medical care.

To prevent development of constipation, particularly with clozapine, it is useful to minimize the doses and number of contributory medications such as other anticholinergic medications and opioids. Activity and exercise should be encouraged to stimulate motility. A stool softener (e.g., docusate, Colace) or psyllium (e.g., Metamucil) can be started for patients at increased risk (e.g., older patients, patients treated with clozapine).

If constipation does develop, initial treatment can include stool softeners (e.g., docusate, Colace) or osmotic laxatives (e.g., lactulose, Enulose, polyethylene glycol, Miralax, bisacodyl, Dulcolax). Second line treatments include stimulant laxatives (e.g., Senna, Senokot, Senna tea, cascara, sodium picosulfate). If constipation persists, an enema (e.g., Fleet) should be considered. A combination of treatments may be needed to treat constipation and then to prevent its recurrence.

Hepatic effects have also been reported with antipsychotic medications (U.S. Department of Health and Human Services; U.S. National Library of Medicine 2017), including elevation of liver enzyme levels and cholestatic jaundice. Cholestatic jaundice is rare and has been primarily reported with chlorpromazine (U.S. Department of Health and Human Services; U.S. National Library of Medicine 2018). It usually occurs within the first month after the initiation of treatment and generally requires discontinuation of treatment. However, given the relative infrequency of antipsychotic-induced jaundice, other etiologies for jaundice should be evaluated before the cause is judged to be antipsychotic medication.

Hematological Effects

Hematological effects are of greatest concern with clozapine; however, they have also been reported with other antipsychotic agents and may include inhibition of leukopoiesis, purpura, hemolytic anemia, and pancytopenia (Balon and Berchou 1986; Pisciotta 1969). For example, with chlorpromazine, transient benign leukopenia (white blood cell [WBC] count < 3,500/mm³) is common whereas agranulocytosis has been reported in 0.08% of patients, typically within the first few months of treatment (Pisciotta 1969).

The etiology of agranulocytosis with clozapine is unclear, but a complex polygenic trait appears likely, perhaps involving the human leukocyte antigen locus or a group of hepatic transporter genes (de With et al. 2017; Legge et al. 2017). Initial estimates suggested that agranulocytosis would develop in 1-2% of patients treated with clozapine, with fatal agranulocytosis in approximately 15% of those individuals (Alvir et al. 1993; Honigfeld et al. 1998). However, data from the initial five years of monitoring through clozapine registries showed a rate of agranulocytosis of 0.38% with death occurring in only 3.1% of those cases (Honigfeld et al. 1998). A recent meta-analysis suggests an incidence of severe neutropenia in 0.9% of clozapine-treated patients with a case fatality rate for individuals with severe neutropenia of 2.1% (Myles et al. 2018). For clozapine-treated patients as a group, the incidence of death due to severe neutropenia was 0.013% (Myles et al. 2018), suggesting that clozapine is quite safe with appropriate monitoring. Nevertheless, patients who are receiving clozapine should be advised to report any sign of
infection immediately (e.g., sore throat, fever, weakness, lethargy) so that a decision can be made about obtaining additional evaluation.

If severe neutropenia does develop, it is usually reversible if clozapine is discontinued immediately and secondary complications (e.g., sepsis) are given intensive treatment. Granulocyte colony stimulating factor has been used to accelerate granulopoietic function and shorten recovery time (Lally et al. 2017c).

Although there have been reports of successful resumption of clozapine after severe neutropenia, the risk of recurrence remains high (Lally et al. 2017b; Manu et al. 2018). For patients with a good clinical response to clozapine after multiple unsuccessful trials of other antipsychotic medications, the benefits and risks of rechallenge require thorough consideration and discussion with the patient and involved family members. Under such circumstances, case reports have suggested using granulocyte colony stimulating factor to reduce the risk of recurrence, although evidence is limited (Lally et al. 2017b).

Neurological Side Effects

Acute Dystonia

Medication-induced acute dystonia is defined by the DSM-5 as the "abnormal and prolonged contraction of the muscles of the eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk developing within a few days of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013a). A dystonic spasm of the axial muscles along the spinal cord can result in opisthotonos, in which the head, neck, and spinal column are hyperextended in an arched position. Rarely, acute dystonia can also present as life-threatening laryngospasm, which results in an inability to breathe (Ganesh et al. 2015). Acute dystonia is sudden in onset and painful and can cause patients great distress. Because of its dramatic appearance, health professionals who are unfamiliar with acute dystonia may incorrectly attribute these reactions to catatonic signs or unusual behavior on the part of patients, whereas oculogyric crises can sometimes be misinterpreted as indicative of seizure activity. In individuals treated with FGAs, it is estimated that up to 10% of patients may experience an acute dystonic episode and, with SGAs, rates of acute dystonia may be less than 2% (Martino et al. 2018; Miller et al. 2008; Satterthwaite et al. 2008). Additional factors that increase the risk of acute dystonia with antipsychotic medication include young age, male gender, recent cocaine use, high medication dose, and intramuscular route of medication administration (Spina et al. 1993; van Harten et al. 1999).

For further discussion of acute dystonia, including its treatment, see Guideline Statement 10.

Akathisia

Medication-induced acute akathisia is defined by the DSM-5 as "subjective complaints of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013a). Akathisia is sometimes difficult to distinguish from psychomotor agitation associated with psychosis, leading to a cycle of increasing doses of antipsychotic medication that lead to further increases in akathisia. Even in
mild forms in which the patient is able to control most movements, akathisia is often extremely distressing to patients, is a frequent cause of nonadherence with antipsychotic treatment, and, if allowed to persist, can contribute to feelings of dysphoria and, in some instances, suicidal behaviors. The reported rates of akathisia vary from 10-15% to as many as one-third of patients treated with antipsychotic medication, even when SGAs are used (Juncal-Ruiz et al. 2017; Martino et al. 2018; Mentzel et al. 2017; Miller et al. 2008). For further discussion of akathisia, including its treatment, see Guideline Statement 12.

Neuroleptic-induced Parkinsonism

Neuroleptic-induced parkinsonism is defined by the DSM-5 as "parkinsonian tremor, muscular rigidity, akinesia (i.e., loss of movement or difficulty initiating movement), or bradykinesia (i.e., slowing of movement) developing within a few weeks of starting or raising the dosage of a medication (e.g., a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013a). These symptoms of neuroleptic-induced parkinsonism are dose dependent and generally resolve with discontinuation of antipsychotic medication. It is important to appreciate that neuroleptic-induced parkinsonism can affect emotional and cognitive function, at times in the absence of detectable motor symptoms. As a result, it can be difficult to distinguish the negative symptoms of schizophrenia or concomitant depression from neuroleptic-induced parkinsonism. In addition, emotional and cognitive features of neuroleptic-induced parkinsonism can be subjectively unpleasant and can contribute to poor medication adherence (Acosta et al. 2012; Ascher-Svanum et al. 2006). For further discussion of neuroleptic-induced parkinsonism, including its treatment, see Guideline Statement 11.

Neuroleptic Malignant Syndrome

NMS is characterized by a classic triad of rigidity, hyperthermia, and sympathethic nervous system lability, including hypertension and tachycardia, in the context of exposure to a dopamine antagonist (or withdrawal of a dopamine agonist), typically within 72 hours of symptom development (American Psychiatric Association 2013a; Gurrera et al. 2011; Gurrera et al. 2017). In addition, NMS is associated with an elevated level of serum creatine kinase (typically, at least 4 times the upper limit of normal), tachypnea, change in mental status (e.g., delirium, stupor), and lack of another identified etiology for the symptoms. Notably, however, the onset and clinical features of NMS can vary and may make recognition more difficult. If misdiagnosed and if mistreated, NMS can be fatal (Berman 2011; Rosebush and Stewart 1989; Strawn et al. 2007).

Other diagnostic considerations in patients presenting with possible NMS include malignant catatonia, malignant hyperthermia (in association with anesthetic administration), heat stroke (for which patients treated with antipsychotics have a heightened susceptibility), serotonin syndrome (in patients also taking serotonergic drugs such as selective serotonin reuptake inhibitors), “benign” elevations in the level of serum creatine kinase, fever in association with clozapine treatment, alcohol or sedative withdrawal, anticholinergic syndrome, hyperthermia associated with use of stimulants and hallucinogens, central nervous system infections, limbic encephalitis, and inflammatory or autoimmune

29 >100.4°F or >38.0°C on at least two occasions, measured orally.
NMS has been reported with almost all medications that block dopamine receptors, but high-potency FGAs appear to be associated with a greater risk of occurrence (Schneider et al. 2018, Stübner et al. 2004). Risk is also increased by use of intramuscular formulations of antipsychotic medications, use of higher total drug dosages, or rapid increases in the dosage of the antipsychotic medication (Keck et al. 1989; Sachdev et al. 1997). Additional risk factors for NMS include acute agitation, dehydration, exhaustion, iron deficiency, physical illness, preexisting neurological disability, and a prior episode of NMS (American Psychiatric Association 2013a; Keck et al. 1989; Sachdev et al. 1997; Strawn et al. 2007). Because NMS is rare, with an estimated incidence of 0.01%–0.02% among individuals treated with antipsychotics (Schneider et al. 2018; Stübner et al. 2004), most evidence regarding NMS treatment comes from single case reports or case series. Antipsychotic medications should always be discontinued, and supportive treatment to maintain hydration and to treat the fever and cardiovascular, renal, or other symptoms should be provided (American Psychiatric Association 2013a; Berman 2011; Strawn et al. 2007). NMS is usually self-limited with resolution within a week in the majority of patients; however, prolonged symptoms of NMS do occur and may be associated with use of LAI antipsychotic medications (Caroff and Mann 1988; Caroff et al. 2000). A number of approaches have been used to treat NMS in addition to antipsychotic discontinuation and supportive care although evidence is limited to case reports and case series (Pileggi and Cook 2016; Strawn et al. 2007). Benzodiazepines, such as lorazepam, have been used because of their benefits in treating catatonia and the parallels between malignant catatonia and NMS. As a postsynaptic D2-receptor agonist, bromocriptine has been used to counteract the dopamine antagonist effects of the antipsychotic medication. Dantrolene, a direct-acting skeletal muscle relaxant, has also been used, particularly in severe cases of NMS, because of its benefits in treating malignant hyperthermia. When NMS has not responded to these interventions or when catatonic symptoms persist after the resolution of NMS, case reports suggest that ECT can be beneficial (Caroff et al. 2000; Pileggi and Cook 2016; Strawn et al. 2007; Wittenauer Welsh et al. 2016). Assistance with emergency management of NMS is recommended and can be obtained through NMSContact (https://www.mhaus.org/nmsis/nmscontact/). Once NMS has resolved, caution is needed when resuming an antipsychotic medication because recurrence has been reported (Rosebush and Stewart 1989; Strawn et al. 2007; Susman and Addonizio 1988). Generally, when treatment is resumed, doses are increased gradually, and a medication other than the precipitating agent is used, typically one with a lower potency at blocking dopamine D2 receptors.

Seizures

Among the antipsychotic medications, clozapine is associated with the greatest likelihood of a seizure and patients with a history of an idiopathic or medication-induced seizure may have a higher risk (Alldredge 1999; Devinsky and Pacia 1994; Wong and Delva 2007). Although generalized tonic-clonic seizures are most frequent, other types of seizures may occur. Seizures may also be preceded by myoclonus or drop attacks.
The seizure risk with clozapine is increased by rapid increases in dose, at high blood levels of clozapine (>1000 ng/ml), as well as by higher doses of the drug. The overall seizure rate is 2.8%; with low-dose treatment (<300 mg/day) the risk is 1%, with medium doses (300–599 mg/day) the risk is 2.7%, and with high doses (>599 mg/day) the risk is 4.4% (Devinsky et al. 1991). Therefore, a slow initial titration of clozapine dose is essential, and patients should be cautioned not to drive or engage in other potentially hazardous activities while clozapine is being titrated. In individuals at high risk of seizure, prophylactic treatment with an anticonvulsant medication can be considered.

FGAs can also lower the seizure threshold in a dose-related manner and result in the development of generalized tonic-clonic seizures (Alldredge 1999). Nevertheless, at usual dose ranges, seizure rates are below 1% for all FGAs.

In patients who do experience a seizure while taking clozapine or another antipsychotic medication, neurological consultation will be important delineating the risks of a further seizure, determining whether anticonvulsant therapy (e.g., valproate) is indicated, and collaborating with the psychiatrist in determining whether changes to the patient’s antipsychotic regimen are indicated (Alldredge 1999; Wong and Delva 2007).

**Tardive Syndromes, Including Tardive Dyskinesia**

Tardive syndromes are persistent abnormal involuntary movement disorders caused by sustained exposure to antipsychotic medication, the most common of which are tardive dyskinesia, tardive dystonia, and tardive akathisia (Frei et al. 2018). They begin later in treatment than acute dystonia, akathisia, or neuroleptic-induced parkinsonism and they persist and may even increase, despite reduction in dose or discontinuation of the antipsychotic medication. Typically, tardive dyskinesia presents as "involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles)" (American Psychiatric Association 2013a), whereas tardive dystonia and tardive akathisia resemble their acute counterparts in phenomenology.

Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications (Carbon et al. 2017; Carbon et al. 2018). It occurs at a rate of approximately 4%–8% per year in adult patients treated with FGAs (Carbon et al. 2018; Woods et al. 2010), a risk that appears to be at least three times that observed with SGAs (Carbon et al. 2018; O'Brien 2016; Woods et al. 2010). Although the majority of patients who develop tardive dyskinesia have mild symptoms, a small proportion will develop symptoms of moderate or severe degree. Various factors are associated with greater vulnerability to tardive dyskinesia, including age greater than 55 years; women; presence of a mood disorder, intellectual disability or central nervous system injury; and past or current akathisia, clinically significant parkinsonism, or acute dystonic reactions (Solmi et al. 2018b).

Evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinetic movements may be observed with a reduction in antipsychotic medication dose, which is termed a withdrawal-emergent dyskinesia (American Psychiatric Association 2013a). Furthermore, spontaneous dyskinesias, which are clinically indistinguishable from tardive dyskinesia, have been described in elderly patients and in up to
20% of never-medicated patients with chronic schizophrenia (Blanchet et al. 2004; Fenton et al. 1997; Saltz et al. 1991). In longer-term studies, findings are often confounded by the sequential or concomitant use of more than one antipsychotic medication and the lack of systematic prospective assessments for the presence of a movement disorder (Tarsy and Baldessarini 2006). Nevertheless, evaluation for the presence of tardive syndromes is important to identify them, minimize worsening, and institute clinically-indicated treatment. For further discussion of tardive syndromes, including their treatment, see Guideline Statement 13.

Ophthalmological Effects

The most common ophthalmological effects of antipsychotic medications are related to the anticholinergic effects of these agents and include blurred vision and exacerbation of open-angle glaucoma. Pigmentary retinopathies and corneal opacities can occur with chronic administration of the low-potency medications thioridazine and chlorpromazine, particularly at high doses (e.g., more than 800 mg/day of thioridazine) (Matsuo et al. 2016). With SGAs, including quetiapine, evidence does not suggest any increase in the likelihood of cataract development (Laties et al. 2015; Pakzad-Vaezi et al. 2013). If patients do undergo cataract surgery, however, there have been case reports of intraoperative floppy-iris syndrome in individuals treated with antipsychotic medications, a complication that has been associated with use of medications that block alpha 1 adrenergic receptors (Chatziralli and Sergentanis 2011). Although adverse ophthalmological effects of antipsychotic medications are infrequent, encouraging regular eye care is important to maintaining good vision for individuals with schizophrenia (Viertiö et al. 2007), particularly due to high rates of diabetes and other health conditions that can affect sight.

Other Side Effects

Anticholinergic Effects

The anticholinergic effects of some antipsychotic medications (along with the anticholinergic effects of antiparkinsonian medications, if concurrently administered) can produce a variety of peripheral side effects, including dry mouth, blurred vision, constipation, tachycardia, urinary retention, and effects on thermoregulation (e.g., hyperthermia in hot weather) (Nasrallah and Tandon 2017; Ozbilen and Adams 2009). Central anticholinergic effects include impaired learning and memory and slowed cognition. Because most anticholinergic side effects are mild and tolerable, they are often overlooked. Nevertheless, they can have multiple implications for patients, including impaired quality of life and significant health complications (Salahudeen et al. 2015). For example, dry mouth is associated with an increased risk for multiple dental complications (Singh and Papas 2014) and drinking high-calorie fluids in response to dry mouth can contribute to weight gain. The muscarinic receptor antagonist properties of antipsychotic drugs can be particularly problematic in older individuals and can contribute to problems such as urinary retention, confusion, fecal impaction, and anticholinergic toxicity (with delirium, somnolence, and hallucinations) (Nasrallah and Tandon 2017). Anticholinergic properties of antipsychotic or antiparkinsonian medications can also precipitate acute angle-closure glaucoma (Lachkar and Bouassida 2007), although patients with treated glaucoma seem to be able to tolerate these medications with careful monitoring (Bower et al. 2018).
The propensity of an antipsychotic medication to cause anticholinergic effects should be considered when choosing an antipsychotic agent initially, particularly in older individuals or those with physical conditions that may confer a greater risk of anticholinergic complications. In selecting a medication, it is also important to keep in mind the total anticholinergic burden from antipsychotic medications, antiparkinsonian medications, urologic medications (e.g., oxybutynin), non-selective antihistamines (e.g., hydroxyzine, diphenhydramine), and other medications with anticholinergic side effects. For this reason, antiparkinsonian medications with anticholinergic properties are not typically administered on a prophylactic basis. When anticholinergic side effects do occur, they are often dose-related and thus may improve with lowering of the dose or administering the medications that have anticholinergic properties in divided doses.

For additional discussion of anticholinergic properties of antiparkisonian medications, see Guideline Statement 11.

Fever

Fever (>38°C) should prompt assessment for possible etiologies including NMS or infection. In hot weather, the possibility of heat stroke should be considered in patients who do not have access to air-conditioned environments due to the increased risk of heat-related events in individuals with psychiatric illness (Bouchama et al. 2007) and the effects of some antipsychotics and anticholinergic agents on thermoregulation (Martin-Latry et al. 2007). In patients who are treated with clozapine, a brief self-limiting fever may occur during the first few weeks of treatment and responds to supportive measures (Bruno et al. 2015; Lowe et al. 2007; Pui-yin Chung et al. 2008). However, it is also essential to assess for the presence of potentially life-threatening complications, including NMS, agranulocytosis, and myocarditis.

Sedation

Sedation is a very common side effect of antipsychotic medications (Citrome 2017a; Leucht et al. 2013). This effect may be related to antagonist effects of those drugs on histamine, adrenergic, and dopamine receptors (Michl et al. 2014). Sedation is most pronounced in the initial phases of treatment, since many patients develop some tolerance to the sedating effects with continued administration. For agitated patients, the sedating effects of these medications in the initial phase of treatment can have therapeutic benefits. Bedtime sedation can also be desirable for patients who are having difficulty sleeping. However, persistent sedation, including daytime drowsiness and increased sleep time, can interfere with social, recreational, and vocational function. Lowering of the daily dose, consolidation of divided doses into one evening dose, or changing to a less sedating antipsychotic medication may be effective in reducing the severity of sedation. Coffee or other caffeine can be helpful in the morning, but can also interact with medications (e.g., contribute to tachycardia, raise blood levels of medications including clozapine). Adding a stimulant medication is not typically helpful and can lead to additional side effects. If sedation or the risk of sedation is significant (e.g., during initial clozapine titration), patients should be cautioned not to drive or engage in potentially hazardous activities.
**Sialorrhea**

Sialorrhea (or hypersalivation) is a frequent side effect of clozapine (Maher et al. 2016) but can also be observed with other antipsychotic medications (Essali et al. 2013). Its etiology is unclear; it likely relates to decreased saliva clearance although actions on muscarinic or α-adrenergic receptors have also been postulated (Ekström et al. 2010). Sialorrhea can contribute to reductions in quality of life and can also be associated with complications such as aspiration pneumonia. During the day, patients can be encouraged to chew sugarless gum, which stimulates the swallowing reflex. Because sialorrhea may be more bothersome at night, patients may be advised to place a towel on their pillow and change to a clean towel in the middle of the night to minimize discomfort. Pharmacological approaches to address sialorrhea come from small studies and case reports and include use of low dose or topical anticholinergic medications, such as glycopyrrolate or sublingual ophthalmic atropine 1% drops. However, since clozapine and other antipsychotics can have significant anticholinergic properties and anticholinergics have small effects on sialorrhea, the use of agents with added anticholinergic effects should be approached cautiously. Terazosin and, in severe refractory cases, botulinum toxin have also been used (Bird et al. 2011; Liang et al. 2010; Man et al. 2017).

**Weight Gain**

Weight gain occurs with most antipsychotic agents and appears to relate to actions of these medications as histamine H1 receptor antagonists, although actions on serotonin and muscarinic receptors may also play a role (He et al. 2013; Kroeze et al. 2003; Michl et al. 2014; Olten and Bloch 2018). Reviews and meta-analyses have compared average weight gains with antipsychotic treatment and the proportion of patients who gain 7% of body weight or more (Bak et al. 2014; Leucht et al. 2013; Zhang et al. 2013). Nevertheless, there is substantial variability in the amount of weight gain that will occur in an individual patient who is treated with a specific antipsychotic medication. Typically, weight gain is progressive over the first 6 months of treatment, although some patients continue to gain weight indefinitely (Alvarez-Jimenez et al. 2008). In identifying individuals with schizophrenia who experience weight gain with antipsychotic treatment, self-reported awareness may be less effective than objective measurement (Gao et al. 2016).

Obesity, in general, can contribute to an increase in risk for mortality and morbidity including increased rates of cardiovascular disease, hypertension, cancers, diabetes, osteoarthritis, and sleep apnea (Aune et al. 2016; Bellou et al. 2018; Jehan et al. 2018; Lauby-Secretan et al. 2016; Stringhini et al. 2017). Consequently, weight gain with antipsychotic medications is also likely to contribute to an increase in physical health conditions and mortality. Prevention of weight gain should, thus, be a high priority, because weight loss is difficult for most patients. Efforts should be made to intervene proactively with weight gain of 5 to 10 pounds, as people who are obese rarely lose more than 10% of body weight with weight loss regimens.

A number of studies have been done to evaluate the effectiveness of specific interventions to prevent or treat antipsychotic-induced weight gain (Caemmerer et al. 2012; Das et al. 2012; de Silva et al. 2016; Giersch et al. 2014; Mahmood et al. 2013; Manu et al. 2015; Mizuno et al. 2014; Mukundan et al. 2010; Zheng et al. 2015). Nutritional interventions have shown small but consistent benefits (Bonfioli et al. 2012), although patients who are willing to enroll and able to adhere to such studies may not be
representative. Nevertheless, nutritional approaches may be suggested for their benefits for overall health as well as for weight. Such approaches include specialized mental health interventions, in-person community interventions (e.g., Weight Watchers), services that include meal delivery (e.g., Jenny Craig), or internet-based interventions (e.g., Omada Health). In addition, some programs have begun to integrate dieticians into the treatment team, given the nutritional challenges that exist for many individuals with serious mental illness (Teasdale et al. 2017). Other non-pharmacological approaches that have been studied include exercise and cognitive behavioral therapy approaches (Bonfio et al. 2012; Caemmerer et al. 2012; Das et al. 2012). In collaboration with the patient’s primary care clinician, medication strategies for weight loss can be considered. Of the pharmacological treatments that have been assessed, metformin has been studied most often. It has been shown to be safe in individuals without hyperglycemia, shows modest benefits on weight (with average weight loss of 3-4 kg), and can reverse metabolic abnormalities in patients with obesity or other metabolic problems (Das et al. 2012; de Silva et al. 2016; McGinty et al. 2016; Mizuno et al. 2014; Siskind et al. 2016; Zheng et al. 2015; Zhuo et al. 2018). However, most studies have been small and follow-up periods have not been longer than 6 months. Modest benefit has also been seen in a number of small studies of topiramate (Mahmood et al. 2013; Mizuno et al. 2014; Zhuo et al. 2018) and other medications have been examined in small trials or case series with less consistent findings (Mizuno et al. 2014). This limited evidence and modest benefit of these pharmacological treatments needs to be considered in light of potential adverse effects.

Another consideration for a patient who has experienced significant weight gain with antipsychotic treatment is a change to a medication with lower weight-gain liability. When possible, other medications that can cause weight gain (e.g., valproate) should be tapered and discontinued. Such decisions need to consider the extent of the patient’s response to the current medication regimen, the risks to the patient if relapse occurs with a medication change, and the likelihood that a medication change will be beneficial in terms of weight loss or other side effects (Manu et al. 2015; Mukundan et al. 2010; Newcomer et al. 2013). In any patient with weight gain, it is also important to assess for other contributors to metabolic syndrome (Mitchell et al. 2012; Mitchell et al. 2013b).

The benefits of exercise appear to be small in terms of weight loss in individuals with schizophrenia (Firth et al. 2015; Pearsall et al. 2014; Vancampfort et al. 2017). Nevertheless, many individuals with schizophrenia do not engage in physical activity (Stubb et al. 2016; Vancampfort et al. 2016) and exercise can be suggested for its benefits to overall health, improved cardiorespiratory fitness and other aspects of functioning (Dauwan et al. 2016; Firth et al. 2015; Firth et al. 2017; Vancampfort et al. 2017).

*Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement*

**Benefits**

Use of an antipsychotic medication in the treatment of schizophrenia can improve positive and negative symptoms of psychosis (high strength of research evidence) and can also lead to reductions in depression and improvements in quality of life and functioning (moderate strength of research evidence). Meta-analysis of double-blind, randomized, placebo-controlled trials showed a medium effect size for overall efficacy (Leucht et al. 2017), with the greatest effect on positive symptoms. The rates of achieving any response or a good response were also significantly greater in those who received
an antipsychotic medication. In addition, the proportion of individuals who dropped out of treatment for
any reason and for lack of efficacy was significantly less in those who were treated with an antipsychotic
medication. Research evidence from head-to-head comparison studies and network meta-analysis
(McDonagh et al. 2017) showed no consistent evidence that favored a specific antipsychotic medication,
with the possible exception of clozapine in improving core illness symptoms and preventing significant
suicide attempts or hospitalization to prevent suicide.

Harms

The harms of using an antipsychotic medication in the treatment of schizophrenia include sedation, side
effects mediated through dopamine receptor blockade (e.g., acute dystonia, akathisia parkinsonism,
tardive syndromes, neuroleptic malignant syndrome, hyperprolactinemia), disturbances in sexual
function, anticholinergic effects, weight gain, glucose abnormalities, hyperlipidemia, orthostatic
hypotension, tachycardia, and QTc prolongation. Clozapine has additional harms associated with its use
including sialorrhea, seizures, neutropenia (which can be severe and life-threatening), myocarditis, and
cardiomyopathy. Among the antipsychotic medications, there is variability in the rates at which each of
these effects occurs and no specific medication appears to be devoid of possible side effects.

Patient Preferences

Clinical experience suggests that many patients are cooperative with and accepting of antipsychotic
medications as part of a treatment plan. A survey of patient preferences reported that patients viewed
an ability to think more clearly and an ability to stop hallucinations or paranoia as important efficacy-
related reasons to take an antipsychotic medication (Achtyes et al. 2018). However, patients also
reported concerns about side effects, particularly weight gain, sedation, and restlessness as reasons that
they may not wish to take antipsychotic medications. Some patients may also choose not to take an
antipsychotic medication when they are feeling well or if they do not view themselves as having a
condition that requires treatment. Some patients may also prefer one medication over another
medication on the basis of prior treatment experiences or other factors.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms.
Although harms of antipsychotic medications can be significant, the impact of schizophrenia on patient's
lives is also substantial and consistent benefits of antipsychotic treatment were found. Harms of
treatment can be mitigated by selecting medications based on individual characteristics and preferences
of patients as well as by choosing a medication based on its side effect profile, pharmacological
characteristics, and other factors. For clozapine, the additional benefits of treatment were viewed as
outweighing the additional rare but serious harms and the need for ANC monitoring to reduce the
likelihood of severe neutropenia. (For additional discussion of the research evidence, see Appendix C,
Statement 4.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this
recommendation.
Review of Available Guidelines from Other Organizations

Information from other guidelines is consistent with this guideline statement. Other guidelines on the treatment of schizophrenia (BAP, CSG, NICE, PORT, RANZCP, SIGN, WFSBP) all recommend use of an antipsychotic medication in the treatment of schizophrenia with the selection of a specific medication on an individualized basis with consideration of medication characteristics, patient characteristics, and patient preferences (Addington et al. 2017a, 2017b; Barnes et al. 2011; Buchanan et al. 2010; Crockford and Addington 2017; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Pringsheim et al. 2017; Scottish Intercollegiate Guidelines Network 2013). Each guideline also recommends the need for monitoring during the course of treatment to assess therapeutic response and treatment-related side effects.

Quality Measurement Considerations

In clinical practice, almost all individuals with schizophrenia are offered an antipsychotic medication. Thus, a quality measure is unlikely to enhance outcomes if it only examines whether an individual with schizophrenia receives antipsychotic treatment.

The importance of treatment with antipsychotic medication for an individual with schizophrenia is, however, implied by the NQF endorsed measure (NQF #1879) "Adherence to Antipsychotic Medications for Individuals with Schizophrenia." This measure is aimed at assessing whether an antipsychotic medication was continued once it was begun but does not determine the proportion of individuals with schizophrenia who receive treatment, per se. Instead, for individuals who are at least 18 years of age and who have a diagnosis of schizophrenia or schizoaffective disorder, this measure assesses the percentage who have been prescribed an antipsychotic medication (as reflected by at least two such prescriptions being filled) and who had a proportion of covered days of at least 0.8 during a 12 consecutive month measurement period. By requiring ongoing prescribing of antipsychotic medication, this measure is more likely to be associated with improvements in outcomes for patients. Nevertheless, this measure does have several limitations. Specifically, it examines whether a medication has been prescribed as reflected by pharmacy claims data or electronic prescription orders, but such measures do not guarantee treatment adherence. For instance, a prescriber could submit an antipsychotic medication prescription and the patient could fill the prescription at the pharmacy, but the patient may not actually take the medication. This measure also does not determine the adequacy of the medication dose and could be met through continuous prescriptions of a sub-therapeutic dose of antipsychotic.

In addition, determining the proportion of covered days in a 12 consecutive month period can be computationally difficult, particularly when patients have transitions in care between settings or treatment providers or when they are receiving more than one antipsychotic medication.

Quality measures, quality improvement initiatives, or electronic decision supports may be appropriate for monitoring side effects of antipsychotic treatment. Evidence suggests that rates of guideline concordant monitoring are low for metabolic risk factors including lipids, diabetes, and weight (Mitchell et al. 2012). Several measures endorsed by NQF address such monitoring. NQF #1932 "Diabetes Screening for People With Schizophrenia or Bipolar Disorder Who Are Using Antipsychotic Medications" measures "The percentage of patients 18-64 years of age with schizophrenia or bipolar disorder, who
were dispensed an antipsychotic medication and had a diabetes screening test during the measurement year." Because this measure is focused on screening, it excludes monitoring of individuals who had diabetes in the measurement year or in the preceding year. NQF #1927 "Cardiovascular Health Medications" measures "The percentage of individuals 25 to 64 years of age with schizophrenia or bipolar disorder who were prescribed any antipsychotic medication and who received a cardiovascular health screening during the measurement year" where cardiovascular health screening consists of "one or more LDL-C screenings performed during the measurement year." Individuals are excluded from this screening measure for having evidence of pre-existing cardiovascular disease as defined by precise criteria in the measure text. Presently, the specific elements of these criteria can often be challenging to determine from structured EHR documentation. Two additional NQF approved measures (NQF #1933 and NQF #1934) address cardiovascular and diabetes monitoring, respectively, for individuals with pre-existing cardiovascular disease or diabetes. Each of these measures is limited to individuals who are 18 to 64 years of age. The cardiovascular monitoring measure requires that individuals receive "an LDL-C test performed during the measurement year" whereas the diabetes monitoring measure requires "One or more HbA1c tests and one or more LDL-C tests performed during the measurement year". These measures have been tested for feasibility, usability, reliability, and validity at the health plan, integrated delivery system, and population level. Individual providers or facilities would not be held accountable for the degree of quality with which this care is delivered. In other words, if a clinician doesn't follow the numerator because of the exclusion, it would be on the measure entity to determine appropriateness. Also, providers and facilities with patients who utilized hospice services or elected to use hospice benefits any time during the measurement year, which can be challenging to determine in many electronic record systems, should not be problematic for the population-based analyses.

Statement 5

APA recommends (1B) that patients with treatment-resistant schizophrenia be treated with clozapine.*

Implementation

Identification of Treatment-Resistant Schizophrenia

Clozapine is recommended for individuals with treatment-resistant schizophrenia but there is considerable variation in definitions of treatment-resistant schizophrenia in clinical trials and in practice (Howes et al. 2017). A typical definition is that a patient's symptoms have shown no response or partial and suboptimal response to two antipsychotic medication trials of at least six weeks each at an adequate dose of medication and some definitions specify using medications from different classes (e.g., SGA versus FGA).

The Treatment Response and Resistance in Psychosis (TRRIP) Working Group conducted a detailed systematic review of clinical trials in treatment-resistant schizophrenia and used a consensus-based

* 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.
approach to establish minimum and optimum criteria for identifying treatment-resistant schizophrenia and guiding future research (Howes et al. 2017). In addition to a diagnosis of schizophrenia, the identification of treatment-resistant schizophrenia rests on the persistence of significant symptoms despite adequate pharmacological treatment (Howes et al. 2017). More specifically, the TRRIP Working Group recommends that symptoms be of at least 12 weeks duration in total, at least moderate severity, and associated with at least moderate functional impairment as determined by validated rating scales (e.g., PANSS, BPRS, SANS, SAPS for symptoms and a score < 60 on the SOFAS as a measure of functioning). If a prospective medication trial of at least 6 weeks at adequate dose has not led to symptom reduction of more than 20%, this provides additional evidence of treatment resistance. It is helpful to note whether the persistent symptoms include positive, negative, or cognitive symptoms, because responses to these symptom domains may differ.

In terms of treatment adequacy, the TRRIP Working Group recommends that at least two antipsychotic trials should have been conducted with different antipsychotic medications with at least 6 weeks at a therapeutic dosage of medication for each and with adherence of at least 80% of prescribed dosages (Howes et al. 2017). A therapeutic dosage of medication was defined as the midpoint of the target range for acute treatment of schizophrenia according to the manufacturer’s product labelling or the equivalent of at least 600 mg of chlorpromazine per day (Howes et al. 2017). (For tables of dose equivalents, see College of Psychiatric and Neurologic Pharmacists 2019; Leucht et al. 2014; Leucht et al. 2015; Rothe et al. 2018.) The consensus criteria include at least one antipsychotic plasma level to assess adherence, obtaining information on adherence from at least 2 sources (e.g., pill counts, dispensing chart reviews, patient/carer reports), and obtaining information on past treatment response from patient/carer reports and other sources. It should also be noted that a medication trial that is truncated in terms of duration or dosage because of poor tolerability cannot be viewed as an adequate trial.

Initiation of Treatment with Clozapine

After a patient is identified as having treatment-resistant schizophrenia, the clinician should engage the patient in discussion about clozapine treatment. Most patients value an ability to think more clearly and stop hallucinations or delusions in deciding about medication changes (Achtyes et al. 2018) and most patients who receive clozapine view it positively. For example, one large survey of individuals with schizophrenia or schizoaffective disorder who were taking an antipsychotic medication found that the vast majority of those taking clozapine adhered to treatment and found it helpful, whereas only approximately 5% found it was not helpful. In contrast, most other antipsychotic medications were viewed less positively (Siskind et al. 2017a). Nevertheless, it is important to identify patient concerns about clozapine and address them insofar as is possible. For example, patients may express concerns about the burdens of required blood work and may encounter logistical barriers such as transportation (Farooq et al. 2019; Gee et al. 2017; Verdoux et al. 2018). However, they may be willing to consider clozapine if logistical barriers can be overcome or if given the information that blood monitoring requirements become less frequent over time. Concerns about other side effects, such as weight gain or somnolence, may also contribute to a reluctance to switch to clozapine (Achtyes et al. 2018). Open discussion of these side effects can be helpful with a well-defined plan for monitoring as treatment proceeds. Peer-run support groups that directly address living with side effects can help patients
develop strategies for coping with side effects. Clinicians may also have concerns about clozapine that can serve as a barrier to treatment. For example, many clinicians have limited experience in using clozapine and sometimes express concerns about paperwork burdens, patient adherence with monitoring, and clozapine side effects (Farooq et al. 2019; Gee et al. 2017; Verdoux et al. 2018; Warnez and Alessi-Severini 2014). Many clinicians overestimate the likelihood of severe neutropenia and are reluctant to begin clozapine on an outpatient basis (Farooq et al. 2019). Education about the use of clozapine and its side effects can be useful in addressing clinician-related prescribing barriers.

When initiating treatment with clozapine, a slow dose titration is essential to minimize the risks of seizure, orthostatic hypotension, and excessive sedation (HLS Therapeutics 2017). Large rapid increases in clozapine dosage have led to cardiovascular collapse and death, particularly in patients taking respiratory depressant medications such as benzodiazepines. From a starting dose of 12.5 mg once or twice daily, the daily dose of clozapine can be increased by, at most, 25 mg to 50 mg per day to a target dose of 300 mg to 450 mg per day, in divided doses (HLS Therapeutics 2017). Subsequent dose increases, if needed, should be of 100 mg or less, once or twice weekly. Although efficacy is often seen at a dose of 300 to 450 mg per day, some individuals may need higher dosages of clozapine, to a maximum daily dose of 900 mg, for full response. A slower rate of titration may be needed for patients who are older, severely debilitated, or sensitive to side effects.

Monitoring for therapeutic benefits and side effects of clozapine should occur throughout the dose titration phase. (See Guideline Statement 4.) Because titration of clozapine proceeds slowly, the therapeutic benefits may not be noticed immediately and side effects may be more prominent than benefits. Thus, it can be helpful to provide patients with education and reassurance about the expected timetable of therapeutic effects of clozapine.

If clozapine is being resumed after a gap in treatment, it should be restarted at 12.5 mg once or twice daily. If that dosage is well tolerated, the dose may be increased to a therapeutic range more quickly than recommended for initial treatment. If a decision is made to stop clozapine, it is best to taper the dose unless the medication is being stopped for medically urgent reasons (e.g., severe neutropenia, myocarditis, NMS).

Use of Clozapine Levels During Treatment with Clozapine

While the dose of clozapine is being titrated, it can be helpful to obtain plasma levels of clozapine and its major active metabolite, norclozapine (n-desmethylclozapine) (Couchman et al. 2010). Plasma levels can also be helpful if there are questions about medication adherence, less efficacy or more side effects than expected, potential medication interactions, or other factors that may be influencing clozapine levels. Although there is substantial variation between individuals, clozapine levels on a specific dosage will generally be greater in non-smokers than in smokers, in heavy caffeine users than in non-users, in women than in men, and in older individuals than in younger individuals (Carrillo et al. 1998; Ismail et al. 2012). In addition, changing between different generic forms of clozapine can lead to a 5%-10% difference in plasma levels. Levels of clozapine should be drawn at steady state (three days or more after a dose change) and at a trough in medication levels (about 12 hours after the last dose). Typically, patients will receive a bedtime dose of clozapine and then have a level drawn the following morning.
before receiving an additional dose. There is not an absolute level of clozapine that is associated with either efficacy or toxicity (Remington et al. 2013; Spina et al. 2000; Suzuki et al. 2011; VanderZwaag et al. 1996). In most patients, efficacy will be highest at levels greater than 350 ng/ml of clozapine, but some patients will show response or prevention of relapse at levels as low as 200 ng/ml. The risk of developing seizures increases with the plasma level of clozapine but is most significant at levels about 1000 ng/ml. Norclozapine has different pharmacokinetic properties and a somewhat different side effect profile as compared to clozapine. Thus, it is also useful to assess the norclozapine level as well as the level of clozapine. Drug-drug interactions and other changes in clozapine metabolism can affect total levels of clozapine and norclozapine as well as causing a shift in the ratio of clozapine to norclozapine (Couchman et al. 2010). More specifically, a decrease in clozapine to norclozapine ratio may suggest that metabolic pathways (e.g., CYP1A2) are being induced whereas an increase in this ratio suggests enzyme inhibition. In addition, the clozapine to norclozapine ratio can be increased in a non-trough sample or if recent dosages of clozapine have been missed.

As with the results of any laboratory test, interpretation of clozapine and norclozapine levels should consider the clinical context. For example, if a clozapine level is much higher than expected, assess for dose-related side effects and clinical evidence of toxicity. If the patient's clinical status does not suggest signs of clozapine toxicity, then determine the timing of the level (e.g., peak versus trough) and identify any potential for drug interactions, changes in smoking status, or incorrect specimen labeling. If levels are much lower than expected, factors such as poor adherence, rapid metabolism, drug interactions, or changes in smoking status may also be relevant.

Monitoring for Side Effects During Treatment with Clozapine

With clozapine, safety monitoring during treatment is important to minimize the risk of adverse events. The Clozapine REMS Program (www.clozapinerems.com) is required for prescribing of clozapine in the U.S. The REMS program includes required training that must be completed by prescribers (Clozapine REMS 2019a), resource materials (Clozapine REMS 2019b), and a shared patient registry for all clozapine manufacturers' products that permits tracking of ANCs and documentation of decisions about continued treatment. The Clozapine REMS site provides instructions about threshold values for ANCs in hematologically-normal individuals and in those with benign ethnic neutropenia, which is most common in individuals of African descent and associated with normal ANCs that are lower than standard reference ranges (Clozapine REMS 2014). It also describes the required frequencies for ANC monitoring, which vary with ANC values. In patients who have stopped or interrupted treatment with clozapine for 30 days or more, the monitoring frequency for treatment initiation will be needed.

Because the highest risk of severe neutropenia (ANC <500) occurs in the initial month of clozapine treatment (Myles et al. 2018), ANC monitoring is more frequent early in treatment and is required less often with longer treatment duration. The need for ANC monitoring can be a common practical issue for patients due to the time and transportation needed to obtain blood tests at a laboratory. The availability

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30 For Canadian prescribers, use the appropriate Canadian clozapine registry and not the U.S. Clozapine REMS program.
of point-of-care testing for white blood counts may mitigate these barriers for patients and facilitate treatment with clozapine.

In addition to neutropenia, clozapine treatment can be associated with several other important side effects. Potentially serious cardiac complications of clozapine treatment include myocarditis and cardiomyopathy. Myocarditis is infrequent and generally occurs during the first month of treatment whereas cardiomyopathy is rare and generally occurs later in the treatment course (Bellissima et al. 2018; Ronaldson et al. 2015). Myocarditis usually is heralded by shortness of breath, tachycardia, and fever but diagnosis can be challenging due to the non-specific nature of other symptoms, which can include fatigue, chest pain, palpitations, peripheral edema, and hypereosinophilia. In patients who develop myocarditis or cardiomyopathy in conjunction with clozapine treatment, clozapine is typically discontinued. Subsequent decisions about resuming clozapine are individualized and based on the benefits and risks of treatment as compared to other therapeutic alternatives.

In patients who are treated with clozapine, a brief self-limiting fever (>38°C) may also occur during the first few weeks of clozapine treatment and responds to supportive measures (Bruno et al. 2015; Lowe et al. 2007; Pui-yin Chung et al. 2008). However, in a febrile patient, it is essential to assess for the presence of potentially life-threatening complications, including NMS, agranulocytosis, infection, and myocarditis.

Other potentially serious side effects of clozapine treatment include seizures, orthostatic hypotension, and gastrointestinal effects. When seizures occur with clozapine, it is typically with very high doses of clozapine, rapid increases in clozapine dose, or shifts in medication levels (related to drug-drug interactions or effects of smoking on drug metabolism) (Devinsky et al. 1991). Therefore, a slow initial titration of clozapine dose is essential, and patients should be cautioned not to drive or engage in other potentially hazardous activities while clozapine is being titrated. If a seizure does occur with clozapine, dose adjustment may be needed or adjunctive anticonvulsant medication (e.g., valproate) may be considered in conjunction with neurological consultation (Alldredge 1999; Wong and Delva 2007).

Orthostatic hypotension can also occur with clozapine and is most common with treatment initiation. Older patients and patients with peripheral vascular disease or a compromised cardiovascular status may be at particular risk. When severe, orthostatic hypotension can cause syncope, dizziness, or falls.

Patients who experience orthostatic hypotension must be cautioned to sit on the edge of the bed for a minute before standing up, move slowly when going from lying or sitting to standing, and seek assistance when needed. Management strategies for orthostatic hypotension include supportive measures (e.g., use of support stockings, increased dietary salt and fluid intake), reducing the speed of clozapine dose titration, and decreasing or dividing doses of clozapine. As a last resort, administration of the salt/fluid retaining corticosteroid, fludrocortisone, can be considered to increase intravascular volume, while being mindful of the potential for immunosuppressive effects and development of diabetes with this medication (Mar and Raj 2018; Shen et al. 2017). For patients who are receiving concomitant antihypertensive treatment, adjustments to the dose of these medications may be needed.
Gastrointestinal effects of clozapine can also be significant and in some patients associated with fecal impaction or paralytic ileus (Every-Palmer and Ellis 2017; Leung et al. 2017). Thus, the patient should obtain urgent medical care if experiencing constipation that is severe or does not resolve. To prevent development of constipation, it is useful to minimize the doses and number of contributory medications such as other anticholinergic medications and opioids. Activity and exercise should be encouraged to stimulate motility. A stool softener (e.g., docusate, Colace) or psyllium (e.g., Metamucil) can be started for patients at increased risk (e.g., older patients). If constipation does develop, initial treatment can include stool softeners (e.g., docusate, Colace) or osmotic laxatives (e.g., lactulose, Enulose, polyethylene glycol, Miralax, bisacodyl, Dulcolax). Second-line treatments include stimulant laxatives (e.g., Senna, Senokot, Senna tea, cascara, sodium picosulfate). If constipation persists, an enema (e.g., Fleet) should be considered. A combination of treatments may be needed to treat constipation and then to prevent its recurrence.

Side effects related to metabolic syndrome are common and generally observed in the initial months of treatment but can also occur later in treatment. These include weight gain (Alvarez-Jimenez et al. 1995; Leucht et al. 2013; Zhang et al. 2013), hyperlipidemia (Buhagiar and Jabbar 2009; Bushe and Paton 2005; Meyer and Koro 2004; Mitchell et al. 2013a), and glucose dysregulation including development of diabetes mellitus (Hirsch et al. 2017; Ward M and Druss 2015; Whicher et al. 2018; Zhang et al. 2017). Monitoring of BMI, hemoglobin A1c, and lipid levels is important during clozapine treatment as outlined in Table 2 in Guideline Statement 1. If diabetes or hyperlipidemia are identified, these should be treated, typically by the patient’s primary care clinician. When weight gain occurs, it is usually progressive over the first 6 months of treatment, although some patients continue to gain weight indefinitely (Alvarez-Jimenez et al. 1995). Prevention of weight gain should, thus, be a high priority, as weight loss is difficult for most patients. Efforts should be made to intervene proactively with weight gain of 5 to 10 pounds and other medications that can cause weight gain (e.g., valproate) should be tapered and discontinued, when possible. Dietary interventions should be suggested (Bonfioli et al. 2012) such as specialized mental health interventions, in-person community interventions (e.g., Weight Watchers), services that include meal delivery (e.g., Jenny Craig), or internet-based interventions (e.g., Omada Health). In collaboration with the patient’s primary care clinician, metformin or non-stimulant medications for weight loss can be considered. Metformin has been shown to be safe in individuals without hyperglycemia and can reduce body weight and reverse metabolic abnormalities in patients with obesity or other metabolic problems (Das et al. 2012; de Silva et al. 2016; Siskind et al. 2016a; McGinty et al. 2016; Mizuno et al. 2014; Zheng et al. 2015; Zhuo et al. 2018). The benefits of exercise appear to be small in terms of weight loss in individuals with schizophrenia (Firth et al. 2015; Pearsall et al. 2014; Vancampfort et al. 2017). Nevertheless, many individuals with schizophrenia do not engage in physical activity (Stubbs et al. 2016a; Vancampfort et al. 2016b) and exercise can be suggested for its benefits for overall health, improved cardiorespiratory fitness and other aspects of functioning (Dauwan et al. 2016; Firth et al. 2015; Firth et al. 2017; Vancampfort 2017).

Sedation, sialorrhea, and tachycardia are each commonly observed during treatment with clozapine but are generally able to be managed conservatively. Sedation is most pronounced in the initial phases of treatment with clozapine, since many patients develop some tolerance to the sedating effects with
continued administration. However, persistent sedation, including daytime drowsiness and increased
sleep time, can interfere with social, recreational, and vocational function. Lowering of the daily dose,
consolidating divided doses into one evening dose, or changing to a less sedating antipsychotic
medication may be effective in reducing the severity of sedation. Coffee or other caffeine can be helpful
in the morning, but can also interact with medications (e.g., contribute to tachycardia, raise blood levels
of medications including clozapine). Adding a stimulant medication is not typically helpful and can lead
to additional side effects. If sedation or the risk of sedation is significant (e.g., during initial clozapine
titrations), patients should be cautioned not to drive or engage in potentially hazardous activities.

Sialorrhea (or hypersalivation) is also a frequent side effect of clozapine that can contribute to
reductions in quality of life and complications such as aspiration pneumonia. Because sialorrhea may be
more bothersome at night, patients may be advised to place a towel on their pillow and change to a
clean towel in the middle of the night to minimize discomfort. During the day, patients can be
encouraged to chew sugarless gum, which stimulates the swallowing reflex. Pharmacological
approaches to address sialorrhea come from small studies and case reports and include use of low dose
or topical anticholinergic medications, such as glycopyrrolate or sublingual ophthalmic atropine 1%
drops (Bird et al. 2011; Liang et al. 2010; Man et al. 2017). However, since clozapine and other
antipsychotics can have significant anticholinergic properties themselves and anticholinergics have small
effects on sialorrhea, the use of agents with added anticholinergic effects should be approached
cautiously. Terazosin and, in severe refractory cases, botulinum toxin have also been used (Bird et al.
2011; Liang et al. 2010; Man et al. 2017).

Healthy patients can usually tolerate some increase in resting pulse rate, although this may not be the
case for patients with preexisting heart disease. In patients with significant tachycardia (heart rates
above 110 to 120 bpm), an ECG is warranted as is assessment for other potential causes of tachycardia
(e.g., fever, anemia, smoking, hyperthyroidism, respiratory disease, cardiovascular disorders, caffeine,
other stimulants, and side effects of other medications). Early in treatment with clozapine, the possibility
of myocarditis should be considered. If tachycardia is accompanied by pain, shortness of breath, fever,
or signs of a myocardial infarction or heart rhythm problem, emergency assessment is essential.

Management strategies for tachycardia with any antipsychotic medication include reducing the dose of
medication, discontinuing medications with anticholinergic or stimulant properties, and addressing
orthostatic hypotension, if present. Case reports have discussed the use of medications such as beta-
blocking agents for persistent and significant tachycardia with clozapine but data from more rigorous
studies is not available and these medications can contribute to other side effects such as orthostatic
hypotension (Lally et al. 2016a).

Side effects related to dopamine D2 receptor antagonism (e.g., acute dystonia, akathisia, neuroleptic
induced Parkinsonism, NMS, tardive syndromes, hyperprolactinemia) can occur but are less frequent
with clozapine than with many other antipsychotic medications. (see Guideline Statement 4: Treatment-
emergent side effects of antipsychotic medications for additional information on the recognition and
management of these side effects.)
Other Approaches to Treatment-resistant Schizophrenia

For all patients with treatment-resistant schizophrenia, a review of the treatment plan is important to conduct at periodic intervals. (See Guideline Statement 3.) In addition to a review of prior medication trials, it is essential to review the psychosocial treatments that a patient has received and whether addition of one or more psychosocial interventions would be of benefit. For example, some patients may not have received cognitive-behavioral therapy (CBT) as recommended in Guideline Statement 14 or initial benefits of CBT may have faded if CBT was stopped. Under such circumstances, treatment with CBT may be warranted (Morrison et al. 2018). A similar review of potential additions to the treatment plan can occur with other psychosocial treatments.

Optimize Treatment with Clozapine

Although studies suggest that at least one-third of individuals with treatment-resistant schizophrenia will respond to clozapine (Kahn et al. 2018; McEvoy et al. 2006), some patients will not have a complete response. Before concluding that a patient has not responded to clozapine, it is important to assure that an adequate target dose has been reached (typically 300 to 450 mg per day) and that steady state levels of clozapine and norclozapine appear sufficient to produce therapeutic benefit. Although no absolute level of clozapine is associated with efficacy (Remington et al. 2013; Spina et al. 2000; Suzuki et al. 2011; VanderZwaag et al. 1996), if no response is evident and clozapine is well-tolerated, the clozapine dose should be increased to achieve a clozapine level of greater than 350 ng/ml. In general, this dose of medication should be continued for at least 8 weeks to determine response, although further increases in dose can also be made, as tolerated. If there continues to be no evidence of benefit, as for any patient treated with clozapine, the value of the medication should be periodically assessed in terms of the patient’s response, the medication side effects, and the availability of any newer treatment options. Longitudinal use of a quantitative measure (see Guideline Statement 2) can be helpful in assessing functioning and overall response and identifying specific symptoms that have or have not responded to treatment.

Continue Clozapine and Augment with Another Medication or Electroconvulsive Therapy

For individuals who do not respond to clozapine alone, the evidence base for other treatments is limited although a number of options have been tried. Augmentation of clozapine with another medication has shown no significant benefit in double-blind trials although some benefit was noted in open label trials and meta-analyses of trials that were generally of low quality (Barber et al. 2017; Correll et al. 2017b; Galling et al. 2017; Sinclair and Adams 2014; Siskind et al. 2018; Veerman et al. 2014; Wagner et al. 2019). Studies have included augmentation with other antipsychotic medications (FGAs and SGAs), anticonvulsants, and other medications. If a trial of augmentation therapy is undertaken, it is important to consider the potential additive effects of the medications on side effects and the potential for drug-drug interactions. Periodic review of the patient’s medication regimen is also important to identify and reduce or discontinue medications that are not effective, that are no longer necessary, or that are contributing to an inordinate burden of side effects. As noted previously, longitudinal use of a quantitative measure can assist in making such determinations.

There is also evidence for benefits of ECT in combination with clozapine as compared to clozapine alone (Grover et al. 2015; Lally et al. 2016b; Petrides et al. 2015; Pompili et al. 2013; Wang et al. 2018b). Rates
of headache and effects on memory are more frequent with ECT plus clozapine than with clozapine alone; however, symptomatic improvement and rates of remission at the end of an ECT course are significantly greater in the group that received adjunctive ECT. For this reason, ECT could be considered for clozapine-resistant schizophrenia, particularly in patients who also have catatonia or significant suicide risk or who require a rapid response due to the severity of their psychiatric or medical condition. For individuals who show a response to ECT, treatment with ECT on a maintenance basis could be considered as an adjunct to clozapine.

For individuals with treatment-resistant schizophrenia who are unable to tolerate clozapine or not interested in pursuing a trial of clozapine, the limited available evidence suggests no benefit from high doses of antipsychotic medication and treatment related side effects are likely to be increased (Dold et al. 2015). However, a trial of a different antipsychotic medication may be helpful, particularly if there is no response to the most recently used medication. Tables 5 through 6 in Guideline Statement 4 can be consulted to identify other antipsychotic medications with receptor binding profiles or different side effects.

Additional Treatment Considerations

Particularly for patients with negative symptoms or depression, augmentation of antipsychotic therapy with an antidepressant medication may be helpful (Helfer et al. 2016; Stroup et al. 2019). Use of a benzodiazepine, such as lorazepam, is also suggested in patients who exhibit catatonia (Bush et al. 1996b; Fink 2013; Pelzer et al. 2018; Unal et al. 2017). Other augmentation approaches (e.g., antipsychotics, anticonvulsants, benzodiazepines, lithium, other medications) have also been studied although evidence is mixed and primarily from small short-term open-label studies (Correll et al. 2017b; Galling et al. 2017; Ortiz-Orendain et al. 2017). For combination therapy with two antipsychotic medications, data from a large nationwide cohort study suggests that emergency visits and rehospitalization rates may be reduced in individuals receiving polypharmacy as compared to monotherapy (Tiihonen et al. 2019). In addition, there is no evidence that combining drugs is any more harmful than using a single medication, beyond the common side effects from each drug. Nevertheless, if multiple drugs are used, monitoring for benefits and side effects is important and it is preferable if changes in dose are limited to one drug at a time.

Some studies have shown evidence for benefits of ECT in combination with antipsychotic medications other than clozapine (Pompili et al. 2013; Zheng et al. 2016). Particularly in patients who also have catatonia or significant suicide risk or who require a rapid response due to the severity of their psychiatric or medical condition, ECT could be considered. For individuals who show a response to ECT, treatment with ECT on a maintenance basis could be considered. Although studies have also been done with TMS for treatment of hallucinations and for treatment of negative symptoms, there is insufficient evidence of benefit to suggest use of TMS in individuals with schizophrenia at present (Dollfus et al. 2016; Dougall et al. 2015; He et al. 2017).
Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
Use of clozapine in individuals with treatment-resistant schizophrenia can be associated with reductions in psychotic symptoms, higher rates of treatment response, and lower rates of treatment discontinuation due to lack of efficacy (low to moderate strength of evidence (SOE)) as well as lower rates of self-harm, suicide attempts, or hospitalizations to prevent suicide (moderate SOE). Overall rates of hospitalization are also reduced during treatment with clozapine as compared to other oral antipsychotic medications (low SOE). All-cause mortality is also reduced in individuals treated with clozapine as compared to other individuals with treatment-resistant schizophrenia (moderate SOE).

Harms
Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low SOE), clozapine does have a higher risk of study withdrawal due to adverse events than some other SGAs (low SOE). Specific harms of using clozapine include rare but serious effects including severe neutropenia, myocarditis, cardiomyopathy, and NMS. These harms cannot be eliminated but risks of severe neutropenia are lessened by required ANC monitoring. Early attention to and recognition of NMS and cardiac complications of clozapine use may also reduce risk. Seizures are also more frequent with clozapine than other antipsychotics but can be minimized by slow titration of the clozapine dose, avoidance of very high clozapine doses, and attention to pharmacokinetic factors that may lead to rapid shifts in clozapine levels. Constipation can also be significant with clozapine and in some patients associated with fecal impaction or paralytic ileus. Other side effects that are more common with clozapine than other antipsychotic medications include sialorrhea, tachycardia, fever, dizziness, sedation, and weight gain. Rates of hyperglycemia and diabetes may also be increased.

Patient Preferences
Clinical experience suggests that many patients are cooperative with and accepting of clozapine as part of a treatment plan; however, other patients may express concerns about the burdens of required blood work including logistical barriers such as transportation (Farooq et al. 2019; Gee et al. 2017; Verdoux et al. 2018). Concerns about other side effects, such as weight gain or somnolence, may also contribute to a reluctance to switch to clozapine (Achtyes et al. 2018). On the other hand, most patients value an ability to think more clearly and stop hallucinations or delusions in deciding about medication changes (Achtyes et al. 2018; Kuhnigk et al. 2012; Levitan et al. 2015) and most patients who receive clozapine view it positively. For example, one large survey of individuals with schizophrenia or schizoaffective disorder who were taking an antipsychotic medication found that the vast majority of those taking clozapine adhered to treatment and found it helpful, whereas only approximately 5% found it was not helpful. In contrast, most other antipsychotic medications were viewed less positively (Siskind et al. 2017a).

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as far outweighing the potential harms. For individuals with treatment-resistant schizophrenia, the risks of inadequately treated illness are substantial in terms of reduced quality of life (Kennedy et al. 2014) and increased mortality (Cho et al.
2019; Vermeulen et al. 2018; Wimberley et al. 2017) as well as negative effects for informal caregivers (Brain et al. 2018). Even in individuals who have had an inadequate response to other antipsychotic medications, a substantial fraction shows a clinically relevant response to clozapine. With careful monitoring to minimize the risk of harms from clozapine, the benefits of clozapine in patients with treatment-resistant schizophrenia were viewed as significantly outweighing the harms of treatment. (For additional discussion of the research evidence, see Appendix C, Guideline Statement 5.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Practice guidelines (BAP, CSG, NICE, RANZCP, SIGN, WFSBP and PORT) are consistent in recommending clozapine for individuals with treatment-resistant schizophrenia (Barnes et al. 2011; Buchanan et al. 2010; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Scottish Intercollegiate Guidelines Network 2013). In terms of other therapies for treatment-resistant depression, several guidelines (SIGN, WFSBP, BAP) recommend augmentation treatment with an antidepressant for treatment-resistant illness associated with negative symptoms (Barnes et al. 2011; Hasan et al. 2012; Scottish Intercollegiate Guidelines Network 2013). For individuals with catatonia, the WFSBP recommends benzodiazepines and ECT (Hasan et al. 2012). In addition, ECT is mentioned in several guidelines (e.g., SIGN, RANZCP, WFSBP) as being appropriate in individuals with treatment-resistant schizophrenia.

Quality Measurement Considerations

Studies suggest that a significant proportion of individuals with treatment-resistant schizophrenia do not receive treatment with clozapine, although there is significant variation between and within countries (Addington et al. 2012; Keller et al. 2014; Stroup et al. 2014). Thus, internal quality improvement programs may wish to focus on ways to increase use of clozapine in individuals with treatment-resistant schizophrenia and track rates of clozapine use in this patient population. Internal quality improvement programs could also focus on increasing use of quantitative measures to improve identification of individuals with treatment-resistant schizophrenia and support systematic longitudinal tracking of functioning, symptoms, and side effect burdens. Electronic decision support is also less likely to be helpful due to the difficulty in identifying individuals with treatment-resistant illness from EHR structured data elements and providing decision support prompts at an appropriate point in the workflow to enhance clinical decision making.

Statement 6

APA recommends (1B) that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*

* 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.
Implementation

Treatment with clozapine can be effective in reducing suicidal behavior if risk remains substantial despite other treatments. In addition, treatment with clozapine can be effective in reducing rates of suicide attempts and suicide in individuals with schizophrenia, regardless of whether formal criteria for treatment resistance have been met. Risk factors for suicidal behavior in individuals with schizophrenia are described under Guideline Statement 1: Implementation. Although demographic and historical risk factors are static, a number of other risk factors are potentially modifiable and can serve as targets of intervention in constructing a plan of treatment. (See Guideline Statement 3 for additional details.) For details of initiating and monitoring clozapine treatment, see Guideline Statement 5 sections on Initiation of Treatment with Clozapine, Use of Clozapine Levels during Treatment with Clozapine, and Monitoring for Side Effects during Treatment with Clozapine.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

In individuals with schizophrenia who are at significant risk for suicide attempts or suicide, use of clozapine can be associated with lower rates of self-harm, suicide attempts, or hospitalization to prevent suicide (moderate SOE). Additional benefits of clozapine treatment include higher rates of treatment response (low to moderate SOE) and reductions in psychotic symptoms, all-cause mortality, overall hospitalization rates, and treatment discontinuation due to lack of efficacy (low to moderate SOE).

Harms

Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low SOE), clozapine does have a higher risk of study withdrawal due to adverse events than some other SGAs (low SOE). Specific harms of using clozapine include rare but serious effects including severe neutropenia, myocarditis, cardiomyopathy, and NMS. These harms cannot be eliminated but risks of severe neutropenia are lessened by required ANC monitoring. Early attention to and recognition of NMS and cardiac complications of clozapine use may also reduce risk. Seizures are also more frequent with clozapine than other antipsychotics but can be minimized by slow titration of the clozapine dose, avoidance of very high clozapine doses, and attention to pharmacokinetic factors that may lead to rapid shifts in clozapine levels. Constipation can also be significant with clozapine and in some patients associated with fecal impaction or paralytic ileus. Other side effects that are more common with clozapine than other antipsychotic medications include sialorrhea, tachycardia, fever, dizziness, sedation, and weight gain. Rates of hyperglycemia and diabetes may also be increased.

Patient Preferences

Clinical experience suggests that many patients are cooperative with and accepting of clozapine as part of a treatment plan; however, other patients may express concerns about the burdens of required blood work including logistical barriers such as transportation (Farooq et al. 2019; Gee et al. 2017; Verdoux et al. 2018). Concerns about other side effects, such as weight gain or somnolence, may also contribute to a reluctance to switch to clozapine (Achtyes et al. 2018). On the other hand, most patients value an ability to think more clearly and stop hallucinations or delusions in deciding about medication changes (Achtyes et al. 2018; Kuhnigk et al. 2012; Levitan et al. 2015) and most patients who receive clozapine...
view it positively. For example, one large survey of individuals with schizophrenia or schizoaffective disorder who were taking an antipsychotic medication found that the vast majority of those taking clozapine adhered to treatment and found it helpful, whereas only approximately 5% found it was not helpful. In contrast, most other antipsychotic medications were viewed less positively (Siskind et al. 2017a).

Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms. For individuals at significant risk for suicide attempts or suicide despite other treatments, the benefit of clozapine in reducing suicide-related risk is significant. With careful monitoring to minimize the risk of harms from clozapine, the benefit of clozapine in such patients was viewed as significantly outweighing the harms of treatment. (For additional discussion of the research evidence, see Appendix C, Guideline Statement 6.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Other guidelines do not specifically mention the use of clozapine for individuals with schizophrenia who are at substantial risk for suicide attempts or suicide despite other treatment. Guidelines (BAP, CSG, NICE, RANZCP, SIGN, WFSBP and PORT) are consistent, however, in recommending clozapine for individuals with treatment-resistant schizophrenia (Barnes et al. 2011; Buchanan et al. 2010; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations

Studies suggest that a significant proportion of individuals with treatment-resistant schizophrenia do not receive treatment with clozapine, although there is significant variation between and within countries (Addington et al. 2012; Keller et al. 2014; Stroup et al. 2014). Given low utilization of clozapine, in general (Addington et al. 2012; Keller et al. 2014; Stroup et al. 2014), and the high rates of suicidal ideas among individuals with treatment-resistant schizophrenia (Kennedy et al. 2014), it is likely that many individuals at significant suicide risk are not receiving treatment with clozapine. Thus, internal quality improvement programs may wish to focus on ways to increase and track use of clozapine in individuals with schizophrenia who have significant suicide risk that persists despite other treatments. Internal quality improvement programs could also focus on increasing the use of quantitative measures to improve identification and monitoring of individuals with risk factors for suicide. However, a more stringent performance measure related to the use of clozapine is not indicated due to the significant role of patient preferences in determining clozapine use and the difficulty in estimating suicide risk from structured data. Electronic decision support using passive alerts may be able to prompt clinicians to consider clozapine; however, such prompts would depend on accurate and consistent entry of information into structured data elements (e.g., problem lists) about diagnosis as well as suicidal ideation and suicide attempts.
Statement 7

APA suggests (2C) that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments. *

Implementation

Treatment with clozapine can be effective in reducing aggressive behavior if risk remains substantial despite other treatments. Risk factors for aggressive behavior in individuals with schizophrenia are described under Guideline Statement 1: Implementation. Although demographic and historical risk factors are static, a number of other risk factors are potentially modifiable and can serve as targets of intervention in constructing a plan of treatment. (See Guideline Statement 3 for additional details.) For details of initiating and monitoring clozapine treatment, see Guideline Statement 5 sections on Initiation of Treatment with Clozapine, Use of Clozapine Levels during Treatment with Clozapine, and Monitoring for Side Effects during Treatment with Clozapine.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

In individuals with schizophrenia who are at significant risk for aggressive behavior, use of clozapine may reduce the likelihood of aggressive behaviors (low SOE). Additional benefits of clozapine treatment include higher rates of treatment response (low to moderate SOE); reductions in psychotic symptoms, all-cause mortality, overall hospitalization rates, and treatment discontinuation due to lack of efficacy (low to moderate SOE); and lower rates of self-harm, suicide attempts, or hospitalizations to prevent suicide (moderate SOE).

Harms

Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low SOE), clozapine does have a higher risk of study withdrawal due to adverse events than some other SGAs (low SOE). Specific harms of using clozapine include rare but serious effects including severe neutropenia, myocarditis, cardiomyopathy, and NMS. These harms cannot be eliminated but risks of severe neutropenia are lessened by required ANC monitoring. Early attention to and recognition of NMS and cardiac complications of clozapine use may also reduce risk. Seizures are also more frequent with clozapine than other antipsychotics but can be minimized by slow titration of the clozapine dose, avoidance of very high clozapine doses, and attention to pharmacokinetic factors that may lead to rapid shifts in clozapine levels. Constipation can also be significant with clozapine and in some patients associated with fecal impaction or paralytic ileus. Other side effects that are more common with clozapine than other antipsychotic medications include sialorrhea, tachycardia, fever, dizziness, sedation, and weight gain. Rates of hyperglycemia and diabetes may also be increased.

Patient Preferences

Clinical experience suggests that many patients are cooperative with and accepting of clozapine as part of a treatment plan; however, other patients may express concerns about the burdens of required blood

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* 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.
work including logistical barriers such as transportation (Farooq et al. 2019; Gee et al. 2017; Verdoux et al. 2018). Concerns about other side effects, such as weight gain or somnolence, may also contribute to a reluctance to switch to clozapine (Achtyes et al. 2018). On the other hand, most patients value an ability to think more clearly and stop hallucinations or delusions in deciding about medication changes (Achtyes et al. 2018; Kuhngk et al. 2012; Levitan et al. 2015) and most patients who receive clozapine view it positively. For example, one large survey of individuals with schizophrenia or schizoaffective disorder who were taking an antipsychotic medication found that the vast majority of those taking clozapine adhered to treatment and found it helpful, whereas only approximately 5% found it was not helpful. In contrast, most other antipsychotic medications were viewed less positively (Siskind et al. 2017a).

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. For individuals at significant risk for aggressive behavior despite other treatments, there appears to be some benefit of clozapine in reducing aggression risk. In addition, clozapine may lead to indirect reductions in the risk of aggressive behavior by reducing other contributory risk factors for aggression such as hallucinations and delusions. Thus, with consideration of patient preferences and careful monitoring to minimize the risk of harms from clozapine, the benefit of clozapine in such patients was viewed as likely to outweigh the harms of treatment. (For additional discussion of the research evidence, see Appendix C, Guideline Statement 7.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

Review of Available Guidelines from Other Organizations

Information from other guidelines is consistent with this guideline statement. The SIGN, RANZCP, BAP and PORT guidelines all suggest consideration of clozapine for individuals with hostility or aggressive behaviors that does not respond to other interventions (Barnes et al. 2011; Buchanan et al. 2010; Scottish Intercollegiate Guidelines Network 2013; Hasan et al. 2012; Galletly et al. 2016). In addition, guidelines (BAP, CSG, NICE, RANZCP, SIGN, WFSBP and PORT) are consistent in recommending clozapine for individuals with treatment-resistant schizophrenia (Barnes et al. 2011; Buchanan et al. 2010; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations

As a suggestion, this guideline statement is not appropriate for use as a quality measure.

Statement 8
APA recommends (1A) that patients with schizophrenia whose symptoms have improved with antipsychotic medication continue to be treated with an antipsychotic medication. *

* 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.
For individuals with a diagnosis of schizophrenia, there are a number of benefits to continued treatment with antipsychotic medication including reduced risks of relapse (Bowtell et al. 2018; Goff et al. 2017; Hui et al. 2018; Kishi et al. 2019; Thompson et al. 2018), rehospitalization (Tiihonen et al. 2018), and death (Tiihonen et al. 2018). Despite this, maintaining adherence to an antipsychotic medication can be difficult for many patients (Acosta et al. 2012; Shafrin et al. 2016; Valenstein et al. 2006). Barriers, facilitators, and motivators of treatment adherence will differ for each patient. However, issues that may influence adherence include, but are not limited to, forgetting to take doses, difficulties managing complex regimens (e.g., due to cognitive impairment, frequency of doses, or number of medications), side effects that are of particular importance to the patient (e.g., weight gain, akathisia, sexual dysfunction), financial barriers (e.g., cost, insurance coverage), insufficient understanding of medication benefits for symptoms that are important to the patient, high levels of hostility, persecutory delusions, suspiciousness of medications or treatment in general, lack of a perceived need for treatment (e.g., due to feeling good or not viewing self as ill, due to personal, religious, or cultural beliefs), co-occurring conditions (e.g., depression or alcohol, cannabis, or other substance use disorder), prior difficulties with adherence, prior experiences with treatment (e.g., effectiveness, side effects), difficulties in the therapeutic relationship, lack of support from significant others for treatment, or perceptions of stigma about having an illness or taking medication (Acosta et al. 2012; Ascher-Svanum et al. 2006; Czobor et al. 2015; Foglia et al. 2017; García et al. 2016; Haddad et al. 2014; Hartung et al. 2017; Hatch et al. 2017; Higashi et al. 2013; Kane et al. 2013; MacEwan et al. 2016a; Pyne et al. 2014; Shafrin et al. 2016; Velligan et al. 2017; Volavka et al. 2016; Wade et al. 2017).

In assessing adherence, it is important to take a patient-centered approach in inquiring in a non-judgmental way whether the individual has experienced difficulties with taking medication (Haddad et al. 2014). Obtaining information from patient diaries, patient-completed rating scales, pharmacy records, family members, or other collateral sources of information can be useful supplements to subjective patient reporting (Acosta et al. 2012; Haddad et al. 2014; Hatch et al. 2017; Kane et al. 2013). It can also be useful to obtain medication blood levels, if available (e.g., with clozapine). Urine levels of antipsychotic medications can also be used to assess for adherence (Velligan et al. 2006). Tablet counts, monitoring using electronic pill bottle caps, and drug formulations with implanted sensors have also been used to assess adherence with antipsychotic medications (Acosta et al. 2012; Haddad et al. 2014).

In terms of enhancing adherence, a wide range of approaches have been tried. However, evidence on the most effective techniques remains limited (Hartung et al. 2017) and different approaches will likely be needed for different patients. In addition to conducting ongoing monitoring of adherence as treatment proceeds, it can be helpful to focus on optimizing treatment efficacy, addressing side effects and concerns about treatment, simplifying medication regimens, providing information about the illness and its treatments, engaging in shared decision making, fostering a strong therapeutic alliance, and engaging family members and other community and social supports, as appropriate (Acosta et al. 2012; Haddad et al. 2014; Kane et al. 2013; Rezansoff et al. 2017). A checklist that includes barriers, facilitators, and motivators for adherence has been developed and may be helpful in promoting discussion and identifying adherence-related factors in individual patients (Pyne et al. 2014).
For some patients, the formulation of the antipsychotic medication may influence adherence. (See table 3, Guideline Statement 4). For example, rapid dissolving tablets or oral concentrates may be preferable for patients who have difficulty swallowing pills or who are ambivalent about medications and inconsistent in swallowing them. LAI formulations may be preferred by some patients (Heres et al. 2007; Patel et al. 2009; Walburn et al. 2001) and, although evidence is mixed (McDonagh et al. 2017), they may be particularly useful for patients with frequent relapses related to nonadherence.

In addition to monitoring the patient’s adherence with medication during the course of treatment, it is also important to assess the ongoing benefits and side effects of treatment that may indicate a need for adjustments to medication doses or changes in medications. The use of quantitative measures can be helpful in systematically assessing each of these realms. (See Guideline Statement 2.) The optimal dose of medication is one that provides the best medication benefits yet is tolerable in terms of medication side effects. For some patients, adjustments in dose will be required during the course of treatment to maintain this balance. Factors such as addition or discontinuation of interacting medications, changes in smoking status, changes in patient body mass, changes in renal or hepatic status, or changes in drug absorption (e.g., with bariatric surgery) may influence medication pharmacokinetics and require increases or decreases in medication dose. When medications with a long half-life are used and, particularly when LAI antipsychotic medications are used, considerations about changes in dose need to consider the extended actions of these medications to minimize the risk of extended side effects. For this reason, if treatment with a LAI formulation is planned, a trial of oral antipsychotic will typically occur first to assure that medication side effects will be tolerable for the patient. In addition, the specific LAI antipsychotic medications have different protocols for initiating treatment, which makes it important to follow the labelling instructions for a given medication.

Under some circumstances, it may be necessary to consider a change from one antipsychotic medication to another one. For example, a patient may have experienced some degree of response to initial treatment but may still have significant symptoms or difficulties in functioning that would warrant a trial of a different medication. A medication change may also be considered due to patient preferences, medication availability, or side effects. Given the long-term health risks of metabolic syndrome and obesity, weight gain and development of diabetes or metabolic syndrome are common reasons that a change to a different medication may be discussed. In a randomized study that examined the effects of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk, a change to aripiprazole was associated with improvements in non-HDL cholesterol, serum triglycerides, and weight as well as a small reduction in 10-year risk of coronary heart disease but no difference in the odds of having metabolic syndrome (Stroup et al. 2011; Stroup et al. 2013). Individuals who switched to aripiprazole, as compared to those who remained on their initial medication, showed no significant increases in symptoms or hospitalizations but did have a higher rate of discontinuing treatment.

Only a limited amount of research has explored the optimal approach for changing antipsychotic medications when warranted. The typical approach is a gradual cross-taper in which the second antipsychotic medication is begun and gradually increased in dose as the initial antipsychotic medication is gradually tapered. However, the few studies that are available do not suggest differences between gradual discontinuation as compared to immediate discontinuation of the first medication (Takeuchi et
In addition, no differences have been seen between starting the second antipsychotic and discontinuing the first antipsychotic at the same time as compared to starting the second antipsychotic and waiting before discontinuing the first antipsychotic agent (Takeuchi et al. 2017b). Regardless of the approach that is taken, careful monitoring is essential to avoid the risks of reduced adherence and clinical destabilization if a change in medications is undertaken.

Evidence on planned reductions of medication doses is even more limited. Unless a medication requires emergent discontinuation, gradual reductions in doses are preferable with close monitoring for recurrent symptoms.

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Use of an antipsychotic medication that has already been associated with symptom response can maintain improvements in symptoms as well as promoting enhanced functioning and quality of life (high SOE). In contrast, discontinuation of antipsychotic treatment can be associated with increases in symptoms and risk of hospitalization and poorer long-term outcomes including greater mortality in the long-term (low SOE).

**Harms**

The harms of continuing use of an antipsychotic medication can vary depending on whether the patient is experiencing any significant side effects from the medication that would have long-term untoward effects. For patients whose medications are well-tolerated, long-term risks include tardive syndromes from antipsychotic medications. For other patients, long-term risks will vary according to the specific side effect, with metabolic effects of antipsychotic medication serving as a possible contributor to long-term health risks.

**Patient Preferences**

Clinical experience suggests that many patients are cooperative with and accepting of antipsychotic medications as part of a treatment plan. This is particularly true when the medication has been associated with a response in symptoms. Indeed, a survey of patient preferences reported that patients viewed an ability to think more clearly and an ability to stop hallucinations or paranoia as important efficacy-related reasons to take an antipsychotic medication (Achtyes et al. 2018). Patients are also likely to value the long-term benefits that have been shown with continued antipsychotic treatment including reductions in relapses, hospitalizations, and mortality. However, patients also report that concerns about side effects, particularly weight gain, sedation, and restlessness can make them reluctant to take antipsychotic medications on a long-term basis. In addition, some patients may choose not to take an antipsychotic medication when they are feeling well or if they do not view themselves as having a condition that requires treatment.

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. Although harms of antipsychotic medications can be significant, the impact of schizophrenia on patient's lives is also substantial and consistent benefits of continued antipsychotic treatment were found. Harms
of treatment can be mitigated by selecting medications based on individual characteristics and
preferences of patients as well as by choosing a medication based on its side effect profile,
pharmacological characteristics, and other factors. (For additional discussion of the research evidence,
see Appendix C, Statement 8.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this
recommendation.

Review of Available Guidelines from Other Organizations
Information from other guidelines is consistent with this guideline statement. Other guidelines on the
treatment of schizophrenia (BAP, NICE, PORT, SIGN, WFSBP) recommend continued use of an
antipsychotic medication in the treatment of schizophrenia once symptom response has been achieved
(Barnes et al. 2011; Buchanan et al. 2010; Hasan et al. 2013; National Institute for Health and Care
Excellence 2014; Scottish Intercollegiate Guidelines Network 2013). Other guidelines (RANZCP, BAP,
SIGN, NICE) also suggest the use of LAI antipsychotic medications based on patient preference or when
adherence has been poor or uncertain (Barnes et al. 2011; Galletly et al. 2016; National Institute for
Health and Care Excellence 2014; Scottish Intercollegiate Guidelines Network 2013). Use of a gradual
reduction in dose, including a gradual cross-taper when changing medications, is noted by several
guidelines (BAP, NICE, SIGN) along with an emphasis on close monitoring for signs of relapse (Barnes et
al. 2011; National Institute for Health and Care Excellence 2014; Scottish Intercollegiate Guidelines
Network 2013).

Quality Measurement Considerations
See Guideline Statement 4 for a discussion of quality measures related to initiation and ongoing use of
an antipsychotic medication.

Statement 9
APA suggests (2B) that patients with schizophrenia whose symptoms have improved with an
antipsychotic medication continue to be treated with the same antipsychotic medication.*

Implementation
As noted in Statement 8, it is important for treatment with an antipsychotic medication to be
maintained once symptoms have improved. Specifically, for individuals with a diagnosis of
schizophrenia, there are a number of benefits to continued treatment with antipsychotic medication,
including reduced risks of relapse (Bowtell et al. 2018; Goff et al. 2017; Hui et al. 2018; Kishi et al. 2019;
Thompson et al. 2018), rehospitalization (Tiihonen et al. 2018), and death (Tiihonen et al. 2018).
Implicitly, continued treatment with an effective and tolerable medication would be preferable to a risk
of destabilization or treatment discontinuation. This inference is also consistent with clinical
observations that individualizing choice of an antipsychotic medication is important. In clinical trials, a
change to a different medication has been associated with earlier discontinuation of treatment as
compared to continuation of the same antipsychotic medication (Essock et al. 2006; Stroup et al. 2011).

Thus, for most patients, it will be optimal to continue on the same medication.

In some circumstances, however, a change in medication may be indicated based on factors such as patient preference, partial response, or medication side effects. The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) trial demonstrates that individuals who discontinued treatment with a medication in an early phase of the trial, either due to issues with efficacy or tolerability, could still go on to do well with a different medication in a subsequent phase of the trial (McEvoy et al. 2006; Rosenheck et al. 2009; Stroup et al. 2007; Stroup et al. 2009). If a change in antipsychotic medications is warranted, the typical approach is a gradual cross-taper in which the second antipsychotic medication is begun and gradually increased in dose as the initial antipsychotic medication is gradually tapered. (See the Implementation section of Guideline Statement 8.) Regardless of the approach that is taken, careful monitoring is essential to avoid the risks of reduced adherence and clinical destabilization with a change in medication.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

Use of an antipsychotic medication that has already been associated with symptom response can maintain improvements in symptoms as well as promoting enhanced functioning and quality of life. In contrast, changes in antipsychotic treatment can be associated with early treatment discontinuation, increases in symptoms, clinical destabilization, and worsening of treatment tolerability.

Harms

The harms of continuing use of the same antipsychotic medication can vary depending on whether the patient is experiencing any significant side effects from the medication that would have long-term untoward effects. Continuing the same medication could lead to greater long-term risks such as metabolic effects or tardive syndromes from antipsychotic medications, but this would depend on the side effect profile of the medication. In some instances, changing to a different medication could worsen long-term side effect risk rather than reduce such risks.

Patient Preferences

Clinical experience suggests that most patients prefer to continue to take an antipsychotic medication that has led to a response in symptoms. Once they have found a medication that is effective and well-tolerated, many individuals experience anxiety if they are unable to continue on that medication because of realistic concerns about a possible return of symptoms, reductions in functioning, risk of hospitalization, and other potential consequences of medication changes. However, other patients may not wish to remain on a given antipsychotic medication due to concerns about side effects or other factors that make continued treatment difficult.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. Although most patients prefer to stay on the same medication once their symptoms have responded, there are reasons that a change in medication may be indicated and factors such as
medication side effects profiles, medication availability, and patient preferences for specific medications also may play a role in decisions to continue with the same medication. (For additional discussion of the research evidence, see Appendix C, Statement 9.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

Review of Available Guidelines from Other Organizations
Information from other guidelines is consistent with this guideline statement. Other guidelines on the treatment of schizophrenia (SIGN, WFSBP) note that treatment should usually continue with the same antipsychotic medication that led to the best response and had the best individual side effect profile, given the risk of destabilization with switching in an antipsychotic regimen (Hasan et al. 2013; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations
As a suggestion, this guideline statement is not appropriate for use as a quality measure or for electronic decision support. However, health plans may wish to implement internal process measures to assess and reduce rates at which changes to stable medication regimens are made based on non-clinical factors such as pre-authorization requirements or formulary changes.

Statement 10
APA recommends (1C) that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.

Implementation
Medication-induced acute dystonia is defined by the DSM-5 as the "abnormal and prolonged contraction of the muscles of the eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk developing within a few days of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013a). A dystonic spasm of the axial muscles along the spinal cord can result in opisthotonos, in which the head, neck, and spinal column are hyperextended in an arched position. Rarely, acute dystonia can also present as life-threatening laryngospasm, which results in an inability to breathe (Ganesh et al. 2015). Acute dystonia is sudden in onset and painful and can cause patients great distress. Because of its dramatic appearance, health professionals who are unfamiliar with acute dystonia may incorrectly attribute these reactions to catatonic signs or unusual behavior on the part of patients, whereas oculogyric crises can sometimes be misinterpreted as indicative of seizure activity. In individuals treated with FGAs, it is estimated that up to 10% of patients may experience an acute dystonic episode and with SGAs, rates of acute dystonia may be less than 2% (Martino et al. 2018; Miller et al. 2008; Satterthwaite et al. 2008). Additional factors that increase the risk of acute dystonia with antipsychotic medication include young age, male gender, recent cocaine use, high medication dose, and intramuscular route of medication administration (Spina et al. 1993; van Harten et al. 1999).

There are a limited number of clinical studies of anticholinergic medications in acute dystonia associated with antipsychotic therapy. Nevertheless, a large amount of clinical experience suggests that acute
Dystonia can be reversed by administration of diphenhydramine, a histamine receptor antagonist with anticholinergic properties. Typically, it is administered intramuscularly to treat acute dystonia, but it can also be administered intravenously in emergent situations, as with acute dystonia associated with laryngospasm. Alternatively, benztropine can also be administered intramuscularly. Once the acute dystonia has resolved, it may be necessary to continue an oral anticholinergic medication to prevent recurrence, at least until other changes in medications can take place such as reducing the dose of medication or changing to an antipsychotic medication that is less likely to be associated with acute dystonia. Typically, a medication such as benztropine or trihexyphenidyl is used for this purpose due to the shorter half-life of oral diphenhydramine and a need for more frequent dosing. (See Table 10 Guideline Statement 11 for additional details of dosing and use of these medications.) Regardless of the anticholinergic medication that is chosen, it is important to use the lowest dose that is able to treat acute dystonia and continue the anticholinergic medication for the shortest time needed to prevent dystonia from recurring. Medications with anticholinergic effects can result in multiple difficulties for patients, including impaired quality of life and significant health complications (Salahudeen et al. 2015). Dry mouth due to anticholinergic effects is associated with an increased risk for multiple dental complications (Singh and Papas 2014) and drinking high-calorie fluids in response to dry mouth can contribute to weight gain. Medications with anticholinergic effects can also precipitate acute angle-closure glaucoma (Lachkar and Bouassida 2007), although patients with treated glaucoma seem to be able to tolerate these medications with careful monitoring (Bower et al. 2018). Other peripheral side effects of anticholinergic medications can include blurred vision, constipation, tachycardia, urinary retention, and effects on thermoregulation (e.g., hyperthermia in hot weather) (Nasrallah and Tandon 2017; Ozbilen and Adams 2009), whereas central anticholinergic effects include impaired learning and memory and slowed cognition. Older individuals can be particularly sensitive to these anticholinergic effects and can develop problems such as urinary retention, confusion, fecal impaction, and anticholinergic toxicity (with delirium, somnolence, and hallucinations) (Nasrallah and Tandon 2017). In addition, it is important to consider the anticholinergic side effects associated with other medications that a patient is taking such as antipsychotic medications, some antidepressant medications, urologic medications (e.g., oxybutynin), and non-selective antihistamines (e.g., hydroxyzine, diphenhydramine).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

In individuals who have acute dystonia associated with antipsychotic therapy, the use of medications with anticholinergic properties (including diphenhydramine, benztropine, and trihexyphenidyl) can be associated with rapid symptom relief. In addition, continuing treatment with an anticholinergic medication can prevent the return of dystonia until other adjustments to the treatment regimen can be made to minimize the risk of recurrence.

Harms

The harms of using a medication with anticholinergic properties to treat acute dystonia include side effects such as dry mouth, blurred vision, precipitation of acute angle glaucoma, constipation (and in
some cases fecal impaction), tachycardia, urinary retention, effects on thermoregulation (e.g.,
hyperthermia in hot weather), impaired learning and memory, slowed cognition, and anticholinergic
toxicity (with delirium, somnolence, and hallucinations). These harms are likely to be greater in older
individuals and may be augmented in individuals taking other medications with anticholinergic
properties.

**Patient Preferences**
Clinical experience suggests that most patients are very uncomfortable and often frightened by acute
dystonia associated with antipsychotic therapy. As a result, they are typically cooperative with and
accepting of acute treatment with an anticholinergic agent. They may also be willing to take one of
these medications to prevent the return of dystonia. However, some patients may be troubled by side
effects such as blurred vision, dry mouth, and constipation and may wish to avoid more significant side
effects associated with anticholinergic medications.

**Balancing of Benefits and Harms**
The potential benefits of this guideline statement were viewed as far outweighing the potential harms.
For the majority of patients who are experiencing acute dystonia associated with antipsychotic therapy,
the rapid relief of symptoms with anticholinergic treatment outweighs the side effects associated with
these medications, at least on a short-term basis. In patients who experience acute laryngeal dystonia,
rapid administration of a medication with anticholinergic properties, such as diphenhydramine, can be
lifesaving. (For additional discussion of the research evidence, see Appendix C, Statement 10.)

**Differences of Opinion Among Writing Group Members**
Eight writing group members voted to recommend this statement. One writing group member disagreed
with this statement out of concern that a reduction in antipsychotic medication dose or a change in
medication may be preferable to immediate use of an anticholinergic medication in some situations. In
addition, one writing group member expressed concern that the use of the phrase "anticholinergic
medication" in the statement may be misleading because diphenhydramine is typically viewed as an
antihistamine but may be preferable to other anticholinergic medications to treat acute dystonia.

**Review of Available Guidelines from Other Organizations**
The guidelines of the WFSBP are in agreement with this recommendation noting that acute dystonia
responds dramatically to administration of anticholinergic or antihistaminic medication (Hasan et al.
2013). The guideline of the BAP notes that use for acute dystonia "should be determined on an
individual basis, taking account of factors such as the patient’s history of extrapyramidal side effects and
the risk of anticholinergic side effects" (Barnes et al. 2011).

**Quality Measurement Considerations**
This guideline statement is not appropriate for use as a quality measure or as part of electronic clinical
decision support. With reductions in the use of high doses of high-potency FGAs, the frequency of acute
dystonia is significantly reduced. In addition, quality measures developed based on this guideline
statement must specify exclusion and exemption criteria given some patients’ potential for significant
anticholinergic side effects even with short-term treatment. Those patients would be inappropriate to include in the measure’s numerator and possibly denominator.

Statement 11

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.

Implementation

Neuroleptic-induced parkinsonism is defined by the DSM-5 as “parkinsonian tremor, muscular rigidity, akinesia (i.e., loss of movement or difficulty initiating movement), or bradykinesia (i.e., slowing movement) developing within a few weeks of starting or raising the dosage of a medication (e.g., a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms” (American Psychiatric Association 2013a). These symptoms of neuroleptic-induced parkinsonism are dose dependent and generally resolve with discontinuation of antipsychotic medication. It is important to appreciate that neuroleptic-induced parkinsonism can affect emotional and cognitive function, at times in the absence of detectable motor symptoms. As a result, it can be difficult to distinguish the negative symptoms of schizophrenia or concomitant depression from neuroleptic-induced parkinsonism. In addition, emotional and cognitive features of neuroleptic-induced parkinsonism can be subjectively unpleasant and can contribute to poor medication adherence (Acosta et al. 2012; Ascher-Svanum et al. 2006).

There are a number of approaches that can be taken when a patient is experiencing neuroleptic-induced parkinsonism. A reduction in the dose of the antipsychotic medication, if feasible, is often helpful in reducing parkinsonism. In some individuals, it may be appropriate to change the antipsychotic medication to one with a lower likelihood of parkinsonism. (See Table 6, Guideline Statement 4). However, before reducing the dose of medication or changing to another antipsychotic medication, the benefits of reduced parkinsonism should be weighed against the potential for an increase in psychotic symptoms. Careful monitoring for symptom recurrence is always important when making changes or reducing doses of antipsychotic medications and use of quantitative measures can be helpful in this regard (as described in Guideline Statement 3).

The use of an anticholinergic medication is another option, either on a short-term basis, until a change in dose or a change in medication can occur, or on a longer-term basis, if a change in dose or change in medication is not feasible. In most circumstances, an anticholinergic medication will only be started after parkinsonian symptoms are apparent. However, some individuals may be at increased risk of developing parkinsonism (e.g., those with significant parkinsonism with prior treatment) and prophylactic use of an anticholinergic medication may occasionally be warranted.

Typically, a medication such as benztropine or trihexyphenidyl is used to treat neuroleptic-induced parkinsonism because diphenhydramine has a shorter half-life and greater likelihood of sedation. However, oral or intramuscular diphenhydramine can also be used on an acute basis. (See Table 10 for additional details on these medications.) It should also be noted that different symptoms of...
parkinsonism (e.g., rigidity, tremors, akinesia) may have a differential response to anticholinergic medications and different treatment approaches may be needed to address each of these symptoms. If an anticholinergic medication is used, it is important to adjust the medication to the lowest dose that is able to treat the parkinsonian symptoms. In addition, it is also important to use the medication for the shortest time necessary. Medications with anticholinergic effects can result in multiple difficulties for patients, including impaired quality of life and significant health complications (Salahudeen et al. 2015). Dry mouth due to anticholinergic effects is associated with an increased risk for multiple dental complications (Singh and Papas 2014) and drinking high-calorie fluids in response to dry mouth can contribute to weight gain. Medications with anticholinergic effects can also precipitate acute angle-closure glaucoma (Lachkar and Bouassida 2007), although patients with treated glaucoma seem to be able to tolerate these medications with careful monitoring (Bower et al. 2018).
Table 10. Medications for Treatment of Neuroleptic-Induced Parkinsonism

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Amantadine</th>
<th>Benztropine mesylate</th>
<th>Diphenhydramine</th>
<th>Trihexyphenidyl hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Symmetrel</td>
<td>Cogentin</td>
<td>Benadryl</td>
<td>Artane</td>
</tr>
<tr>
<td>Typical use</td>
<td>Parkinsonism</td>
<td>Acute dystonia, Parkinsonism</td>
<td>Acute dystonia, Parkinsonism</td>
<td>Acute dystonia, Parkinsonism</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Uncompetitive NMDA receptor antagonist (weak)</td>
<td>Muscarinic Antagonist</td>
<td>Histamine H1 Antagonist</td>
<td>Muscarinic Antagonist</td>
</tr>
<tr>
<td>Available Preparations</td>
<td>Tablet: 100</td>
<td>Tablet: 0.5, 1, 2 Solution, Injection: 1/mL (2 mL)</td>
<td>Capsule: 25, 50</td>
<td>Oral Elixir: 0.4 /mL (473 mL)</td>
</tr>
<tr>
<td></td>
<td>Tablet, Extended Release: 129, 193, 258 Capsule: 100</td>
<td>Injection: 1/mL (2 mL)</td>
<td>Oral Elixir: 12.5/5 mL</td>
<td>Tablet: 2, 5</td>
</tr>
<tr>
<td></td>
<td>Capsule, Liquid Filled: 100</td>
<td>Oral Solution: 12.5/5 mL, 6.25 /1 mL</td>
<td>Solution, Injection: 50/1 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsule, Extended Release: 68.5, 137</td>
<td>Tablet: 25, 50</td>
<td>Other brand name formulations are available for allergy relief</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral Syrup: 50/5 mL</td>
<td>Solution, Injection: 10-50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical dose range</td>
<td>Immediate Release Tablet or Capsule: 100-300</td>
<td>Tablet: 0.5-6.0</td>
<td>Oral: 75-200</td>
<td>Oral: 5-15</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>86% to 94%</td>
<td>29%</td>
<td>40% to 70%</td>
<td>100%</td>
</tr>
</tbody>
</table>

This table includes information compiled from multiple sources. It is recommended that readers consult product labeling information for authoritative information on these medications. Detailed information on issues such as dose regimen, dose adjustments, medication administration procedures, handling precautions, and storage can also be found in product labeling.

The most common U.S. trade names are included for reference only. At the time of publication, some of these products may only be manufactured as generic products. Other medications or other formulations of the listed medications may be available in Canada.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Amantadine</th>
<th>Benztropine mesylate</th>
<th>Diphenhydramine</th>
<th>Trihexyphenidyl hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak level (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Release: 2-4</td>
<td>Extended Release: 7.5-12</td>
<td>7</td>
<td>1-4</td>
<td>1.3</td>
</tr>
<tr>
<td>Protein binding</td>
<td>67%</td>
<td>95%</td>
<td>76% to 85%</td>
<td>Not known</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily renal</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Not known</td>
</tr>
<tr>
<td>Metabolic enzymes/transporters</td>
<td>Substrate of organic cation transporter 2 (OCT2)</td>
<td>Substrate of CYP2D6 (minor)</td>
<td>Extensively hepatic n-demethylation via CYP2D6; minor demethylation via CYP1A2, CYP2C9 and CYP2C19. Inhibits CYP2D6 (weak).</td>
<td>None known</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Multiple; unknown activity</td>
<td>Not known</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life (hours)</td>
<td>16-17</td>
<td>7</td>
<td>4-8</td>
<td>4</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine 85% unchanged; 0.6% fecal</td>
<td>Urine</td>
<td>Urine (as metabolites and unchanged drug)</td>
<td>Urine and bile</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>No dose adjustments noted in labeling</td>
<td>No dose adjustments noted in labeling</td>
<td>No dose adjustments noted in labeling</td>
<td>No dose adjustments noted in labeling</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Elimination half-life increased with renal impairment.</td>
<td>No dose adjustments noted in labeling</td>
<td>No dose adjustments noted in labeling; however, dosing interval may need to be increased or dosage reduced in older individuals and with renal impairments</td>
<td>No dose adjustments noted in labeling</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Amantadine</td>
<td>Benztropine mesylate</td>
<td>Diphenhydramine</td>
<td>Trihexyphenidyl hydrochloride</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Comments</td>
<td>Negligible removal by dialysis; do not crush or divide extended release products.</td>
<td>Onset of action with IV is comparable to IM.</td>
<td>Total daily dose typically divided into 3-4 doses per day. Maximum daily dose 300 mg for oral and 400 mg for IM/IV, with 100 mg maximum dose for IV/IM. Give IV at a rate of 25 mg/minute. Give IM by deep intramuscular injection, because subcutaneous or intradermal injection can cause local necrosis.</td>
<td></td>
</tr>
</tbody>
</table>
Other peripheral side effects of anticholinergic medications can include blurred vision, constipation, tachycardia, urinary retention, and effects on thermoregulation (e.g., hyperthermia in hot weather) (Nasrallah and Tandon 2017; Ozbilen and Adams 2009), whereas central anticholinergic effects include impaired learning and memory and slowed cognition. Older individuals can be particularly sensitive to these anticholinergic effects and can develop problems such as urinary retention, confusion, fecal impaction, and anticholinergic toxicity (with delirium, somnolence, and hallucinations) (Nasrallah and Tandon 2017). In addition, it is important to consider the anticholinergic side effects associated with other medications that a patient is taking such as antipsychotic medications, some antidepressant medications, urologic medications (e.g., oxybutynin), and non-selective antihistamines (e.g., hydroxyzine, diphenhydramine).

Amantadine is an alternative to using an anticholinergic medication to treat neuroleptic-induced parkinsonism. Studies of amantadine have had small samples but the available evidence and clinical experience suggest that amantadine may have comparable or somewhat less benefit in treating neuroleptic-induced parkinsonism than anticholinergic agents but with fewer side effects (Ananth et al. 1975; Borison 1983; DiMascio et al. 1976; Fann and Lake 1976; Greenblatt et al. 1977; Kelly et al. 1974; König et al. 1996; Mindham et al. 1972; McEvoy 1987; McEvoy et al. 1987; Silver et al. 1995). Common adverse effects with amantadine include nausea, dizziness, insomnia, nervousness, impaired concentration, fatigue, and livedo reticularis. Hallucinations and suicidal thoughts have also been reported as has an increased seizure frequency in individuals with pre-existing seizure disorder (Micromedex 2019).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
In individuals who have neuroleptic-induced parkinsonism, a reduction in signs and symptoms such as rigidity, tremor, and bradykinesia can be of significant benefit whether such a reduction is achieved by reducing the dose of antipsychotic medication, changing to another antipsychotic medication that has less propensity to cause parkinsonism, or using medications with anticholinergic properties to treat the parkinsonism.

Harms
Reducing the dose of an antipsychotic medication or changing to a different antipsychotic medication can be associated with an increase in psychotic symptoms. The harms of using a medication with anticholinergic properties to treat neuroleptic-induced parkinsonism include side effects such as dry mouth, blurred vision, precipitation of acute angle closure glaucoma, constipation (and in some cases fecal impaction), tachycardia, urinary retention, effects on thermoregulation (e.g., hyperthermia in hot weather), impaired learning and memory, slowed cognition, and anticholinergic toxicity (with delirium, somnolence, and hallucinations). These harms are likely to be greater in older individuals and may be augmented in individuals taking other medications with anticholinergic properties.
Patient Preferences

Clinical experience suggests that most patients are bothered by neuroleptic-induced parkinsonism and would like to minimize or eliminate this side effect of antipsychotic medication. However, most patients will also want to minimize the chance that psychotic symptoms will increase. Many patients are also troubled by side effects such as blurred vision, dry mouth, and constipation and may wish to avoid more significant side effects associated with anticholinergic medications. Consequently, the balance of these possible risks and benefits of different approaches to addressing neuroleptic-induced parkinsonism are likely to vary for each individual and his or her risk factors and personal preferences.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms because neuroleptic-induced parkinsonism can affect the patient's quality of life and patients would prefer to address it, if feasible. However, each of the available options for decreasing or eliminating neuroleptic-induced parkinsonism has associated risks and characteristics and preferences of each patient need to be taken into consideration. (For additional discussion of the research evidence, see Appendix C, Statement 11.)

Differences of Opinion Among Writing Group Members

Eight writing group members voted to suggest this statement. One writing group member disagreed with this statement believing that a reduction in antipsychotic medication dose or a change in medication would be preferable to use of an anticholinergic medication.

Review of Available Guidelines from Other Organizations

Statements from other guidelines vary in their approach to neuroleptic-induced parkinsonism. The WFSBP guideline notes that use of SGAs or reductions in medication doses should be the primary treatment for neuroleptic-induced parkinsonism (Hasan et al. 2013). The BAP guideline notes that decisions about the use of anticholinergic medications for neuroleptic-induced parkinsonism should be made on an individual basis but these medications should not be given prophylactically (Barnes et al. 2011). The PORT guideline notes that prophylactic use of antiparkinsonian agents is not warranted in patients treated with SGAs but may be indicated on an individual basis in patients treated with FGAs (Buchanan et al. 2010).

Quality Measurement Considerations

As a suggestion, this statement is not appropriate for use as a quality measure. It is also not appropriate for incorporation into electronic decision support.

Statement 12

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.

Implementation

Medication-induced acute akathisia is defined by the DSM-5 as "subjective complaints of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking
from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or
raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication
used to treat extrapyramidal symptoms" (American Psychiatric Association 2013a). Akathisia is
sometimes difficult to distinguish from psychomotor agitation associated with psychosis, leading to a
cycle of increasing doses of antipsychotic medication that lead to further increases in akathisia. Even in
mild forms in which the patient is able to control most movements, akathisia is often extremely
distressing to patients, is a frequent cause of nonadherence with antipsychotic treatment, and, if
allowed to persist, can contribute to feelings of dysphoria and, in some instances, suicidal behaviors. The
reported rates of akathisia vary from 10%-15% to as many as one-third of patients treated with antipsychotic medication, even when SGAs are used (Juncal-Ruiz et al. 2017; Martino et al. 2018; Mentzel et al. 2017; Miller et al. 2008).

There are a number of approaches that can be taken when a patient is experiencing antipsychotic-induced akathisia. A reduction in the dose of the antipsychotic medication, if feasible, is often helpful in reducing akathisia. In some individuals, it may be appropriate to change the antipsychotic medication to one with a lower likelihood of akathisia. (See Table 6, Guideline Statement 4). However, before reducing the dose of medication or changing to another antipsychotic medication, the benefits of reduced akathisia should be weighed against the potential for an increase in psychotic symptoms. Careful monitoring for symptom recurrence is always important when making changes or reducing doses of antipsychotic medications and use of quantitative measures can be helpful in this regard (as described in Guideline Statement 3).

Benzodiazepine medications, including lorazepam and clonazepam, can also be helpful in the treatment of akathisia. Among other side effects, somnolence and cognitive difficulties can be associated with benzodiazepine use (Lexicomp 2019; Micromedex 2019). In addition, problems with coordination as a result of benzodiazepines can contribute to falls, particularly in older individuals (Donnelly et al. 2017). Although benzodiazepines are much safer than older sedative agents, respiratory depression can be seen with high doses of a benzodiazepine, particularly in combination with alcohol, other sedating medications, or opioids (Hirschtritt et al. 2017). Caution may also be indicated in prescribing benzodiazepines to individuals with sleep apnea, although few studies are available (Mason et al. 2015). Individuals who are treated with a benzodiazepine may also take them in higher amounts or frequencies than intended. In some patients, a sedative, hypnotic, or anxiolytic use disorder may develop, particularly in individuals with a past or current diagnosis of alcohol use disorder or another substance use disorder.

Another option for treatment of akathisia is the beta-adrenergic blocking agent, propranolol (Pringsheim et al. 2018), which is typically administered in divided doses with a total daily dose of 30 mg to 120 mg. When using propranolol, it is important to monitor blood pressure with increases in dose and recognize that taking propranolol with protein-rich foods can increase bioavailability by 50%. In addition, propranolol is metabolized by CYP1A2, CYP2D6, CYP2C19 and CYP3A4, which can contribute to drug-drug interactions. Some literature also suggests that mirtazapine may reduce akathisia in some patients (Perry et al. 2018; Praharaj et al. 2015). In contrast, akathisia tends not to respond to anticholinergic agents (Pringsheim et al. 2018; Rathbone and Soares-Weiser 2006).
Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

**Benefits**

In individuals who have akathisia associated with antipsychotic medication, a reduction in symptoms can be of significant benefit whether such a reduction is achieved by reducing the dose of antipsychotic medication, changing to another antipsychotic medication that has less propensity to cause akathisia, or using a benzodiazepine or a beta-adrenergic blocking agent to treat akathisia.

**Harms**

Reducing the dose of an antipsychotic medication or changing to a different antipsychotic medication can be associated with an increase in psychotic symptoms. The harms of using a benzodiazepine can include somnolence, cognitive difficulties, problems with coordination, and risk of misuse or development of a sedative use disorder. In high doses and particularly in combination with alcohol, other sedating medications, or opioids, respiratory depression may occur. With use of a beta-adrenergic blocking agent, such as propranolol, the primary harm relates to lowering of blood pressure.

**Patient Preferences**

Clinical experience suggests that most patients are bothered by akathisia and, in some instances, very distressed by it. Thus, almost all patients would like to minimize or eliminate this side effect of antipsychotic medication. However, most patients will also want to minimize the chance that psychotic symptoms will increase. They may also be concerned about the possible side effects of medications such as benzodiazepines and beta-adrenergic blocking agents. Consequently, the balance of these possible risks and benefits of different approaches to addressing akathisia are likely to vary for each individual and his or her risk factors and personal preferences.

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms because akathisia can affect patient's quality of life and patients would prefer to address it, if feasible. However, each of the available options for decreasing or eliminating akathisia has associated risks and characteristics and the preferences of each patient need to be taken into consideration. (For additional discussion of the research evidence, see Appendix C, Statement 12.)

**Differences of Opinion Among Writing Group Members**

There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

**Review of Available Guidelines from Other Organizations**

The WFSBP guideline notes that there is some evidence that benzodiazepines are effective in the treatment of akathisia and very limited evidence to support the use of centrally active beta-adrenergic blocking agents in the treatment of akathisia (Hasan et al. 2013).

**Quality Measurement Considerations**

As a suggestion, this statement is not appropriate for use as a quality measure. It is also not appropriate for incorporation into electronic decision support.
Statement 13

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 transporter2 (VMAT2) (e.g., deutetrabenazine, tetrabenazine, valbenazine).

Implementation

Tardive syndromes are persistent abnormal involuntary movement disorders caused by sustained exposure to antipsychotic medication, the most common of which are tardive dyskinesia, tardive dystonia, and tardive akathisia (Frei et al. 2018). They begin later in treatment than acute dystonia, akathisia, or neuroleptic-induced parkinsonism and they persist and may even increase, despite reduction in dose or discontinuation of the antipsychotic medication. Typically, tardive dyskinesia presents as "involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles)" (American Psychiatric Association 2013a), whereas tardive dystonia and tardive akathisia resemble their acute counterparts in phenomenology.

Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications (Carbon et al. 2017; Carbon et al. 2018). It occurs at a rate of approximately 4%–8% per year in adult patients treated with FGAs (Carbon et al. 2018; Woods et al. 2010), a risk that appears to be at least three times that observed with SGAs (Carbon et al. 2018; O'Brien 2016; Woods et al. 2010). Various factors are associated with greater vulnerability to tardive dyskinesia, including age greater than 55 years; women; presence of a mood disorder, intellectual disability, or central nervous system injury; and past or current akathisia, clinically significant parkinsonism, or acute dystonic reactions (Solmi et al. 2018b).

Evaluation for the presence of tardive syndromes is important to identify them, minimize worsening, and institute clinically-indicated treatment. However, evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinetic movements may be observed with a reduction in antipsychotic medication dose, which is termed a withdrawal-emergent dyskinesia (American Psychiatric Association 2013a). Furthermore, spontaneous dyskinesias, which are clinically indistinguishable from tardive dyskinesia, have been described in elderly patients and in up to 20% of never-medicated patients with chronic schizophrenia (Blanchet et al. 2004; Fenton et al. 1997; Saltz et al. 1991). Regular assessment of patients for tardive syndromes through clinical examination or through the use of a structured evaluative tool can aid in identifying tardive syndromes, clarifying their likely etiology, monitoring their longitudinal course, and determining the effects of medication changes or treatments for tardive dyskinesia. (See Table 2, Guideline Statement 1.) The Abnormal Involuntary Movement Scale (AIMS) is an example of such a structured tool (Guy 1976; Munetz and Benjamin 1988), although it should be noted that there is no specific score threshold on the AIMS that suggests a need for intervention.

Although the majority of patients who develop tardive dyskinesia have mild symptoms, a small proportion will develop symptoms of moderate or severe degrees. In such circumstances, a trial of a lower potency or a lower dose of antipsychotic medication can be considered, although evidence for this approach is minimal (Bergman et al. 2017). Assessment for other contributors to a movement disorder is also warranted (Jinnah and Factor 2015; Mehta et al. 2015; Poewe and Djamshidian-Tehrani 2015;
Preskorn et al. 2015; Waln and Jankovic 2015). In addition to a neurological examination and complete  
history of motor symptoms and past and current medications, history and laboratory testing may  
include liver function tests, thyroid function tests, serum calcium, complete blood count, and  
antiphospholipid antibodies. Depending on the results of the history and evaluation, additional studies  
may be indicated (e.g., ceruloplasmin for Wilson disease, brain MRI for basal ganglia changes with  
Huntington’s disease, stroke or other lesions, lumbar puncture for anti-NMDA encephalitis). If dyskinetic  
movements have begun or increased in the context of antipsychotic dose reduction, it is important to  
assess the longitudinal course of symptoms for up to several months as spontaneous reductions or  
resolution of the dyskinesia may occur.

If no contributing etiology is identified and moderate to severe or disabling tardive dyskinesia persists,  
treatment is recommended with a reversible inhibitor of the vesicular monoamine transporter 2  
(VMAT2), which appears to act by depleting monoamine stores. Table 11 shows the characteristics of  
VMAT2 inhibitors that are currently available in the U.S.

Table 11. Reversible inhibitors of human vesicular monoamine transporter type 2.33,34

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Deutetrabenazine</th>
<th>Tetrabenazine</th>
<th>Valbenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name35</td>
<td>Austedo</td>
<td>Xenazine</td>
<td>Ingrezza</td>
</tr>
<tr>
<td>Available Preparations (mg)</td>
<td>Tablet: 6, 9, 12</td>
<td>Tablet: 12.5, 25</td>
<td>Capsule: 40, 80</td>
</tr>
<tr>
<td>Typical dose range (mg/day)</td>
<td>12-18</td>
<td>25-75</td>
<td>40-80</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>80%</td>
<td>75%</td>
<td>49%</td>
</tr>
<tr>
<td>Time to peak level (hours)</td>
<td>3-4</td>
<td>1-2</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Protein binding</td>
<td>60% to 68% (alpha dihydrotetrabenazine (HTBZ)) 59% to 63% (beta-HTBZ)</td>
<td>82% to 85% 60% to 68% (alpha-HTBZ) 59% to 63% (beta-HTBZ)</td>
<td>&gt;99% 64% alpha- HTBZ</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Metabolic enzymes/transporters</td>
<td>Major substrate of CYP2D6, minor substrate of CYP1A2 and CYP3A4</td>
<td>Major substrate of CYP2D6</td>
<td>Major substrate of CYP3A4, minor substrate of CYP2D6</td>
</tr>
</tbody>
</table>

33 This table includes information compiled from multiple sources. It is recommended that readers consult product labeling  
information for authoritative information on these medications. Detailed information on issues such as dose regimen, dose  
adjustments, medication administration procedures, handling precautions, and storage can also be found in product labeling.

34 Source. Austedo (deutetrabenazine) tablets 2018; Ingrezza (valbenazine) 2018; Lexicomp 2019; Micromedex 2019; Xenazine  
(tetrabenazine) tablets 2018

35 The most common U.S. trade names are included for reference only. At the time of publication, some of these products may  
only be manufactured as generic products.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Deutetrabenazine</th>
<th>Tetrabenazine</th>
<th>Valbenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolites</td>
<td>Deuterated alpha and beta HTBZ: Active</td>
<td>Alpha, beta and O-dealkylated HTBZ: Active</td>
<td>alpha-HTBZ: Active</td>
</tr>
<tr>
<td>Elimination half-life (hours)</td>
<td>Deuterated alpha and beta HTBZ: 9-10</td>
<td>Alpha-HTBZ: 4-8 Beta-HTBZ: 2-4</td>
<td>15-22</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (~75%-85% changed); feces (~8% to 11%)</td>
<td>Urine (~75% changed); feces (~7% to 16%)</td>
<td>Urine: 60%; feces: 30%</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Maximum dose of 50 mg daily with moderate to severe impairment (Child-Pugh score 7 to 15)</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>No information available</td>
<td>No information available</td>
<td>Use not recommended in severe renal impairment (CrCl &lt;30 mL/min)</td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>Sedation</td>
<td>Sedation, depression, extrapyramidal effects, insomnia, akathisia, anxiety, nausea, falls</td>
<td>Sedation</td>
</tr>
<tr>
<td>Effect of food on bioavailability</td>
<td>Food effects maximal concentration. Administer with food. Swallow tablets whole and do not chew, crush, or break.</td>
<td>Unaffected by food</td>
<td>Absorption decreased by high fat meals</td>
</tr>
<tr>
<td>Comments</td>
<td>Give in divided doses, increase from initial dose of 12 mg daily by 6 mg per week to maximum dose of 48 mg/day. Retitrate dose for treatment interruptions of more than 1 week. Follow product labeling if switching from tetrabenazine to deutetrabenazine. Do not exceed total daily dose of 36 mg/day (18 mg/dose) in poor CYP2D6 metabolizers or patients taking a strong CYP2D6 inhibitor.</td>
<td>Give in divided doses, increase from initial 25-50 mg dose by 12.5 mg/week to maximum of 150-200 mg. Retitrate dose for treatment interruptions of more than 5 days. Test for CYP2D6 metabolizer status before giving doses &gt; 50 mg/day. Do not exceed 50 mg/day in poor metabolizers or in patients treated with a strong inhibitor of CYP2D6. Avoid use with increased risk of QTc prolongation.</td>
<td>Initiate at 40 mg daily and increase to 80 mg daily after 1 week. Use is not recommended with strong CYP3A4 inducer. A reduced dose is recommended with concomitant use of strong CYP3A4 or CYP2D6 inhibitors or in poor CYP2D6 metabolizers. Avoid use in patients with other risks for QTc prolongation.</td>
</tr>
</tbody>
</table>

36 All VMAT2 inhibitors are contraindicated within 2 weeks of an MAOI, within 20 days of reserpine, or in patients with active suicidal ideas or untreated depression. Tetrabenazine and deutetrabenazine carry a boxed warning related to depression and suicidal ideation in patients with Huntington’s disease.
In general, deutetrabenazine or valbenazine are preferred over tetrabenazine because of the shorter half-life of tetrabenazine. Other factors that may influence choice of a VMAT2 inhibitor relate to hepatic or renal function; tetrabenazine and deutetrabenazine are contraindicated in individuals with hepatic impairment whereas valbenazine is not recommended for use in individuals with severe renal impairment. The metabolism of these medications is also somewhat different. Although all of these medications are substrates for CYP2D6 and CYP3A4, tetrabenazine and deutetrabenazine are major substrates for CYP2D6 whereas valbenazine is a major substrate for CYP3A4. Consequently, the patient’s CYP2D6 metabolizer status or use of concomitant medications that influence these metabolic enzymes may affect the choice of a VMAT2 inhibitor. In terms of side effects, these medications are generally well-tolerated with sedation being most common. In initial studies of tetrabenazine in patients with Huntington’s disease, significant rates of depression were noted as well as concerns about suicidal ideas and behaviors (Shen et al. 2013). However, in the studies of deutetrabenazine and valbenazine in patients with tardive dyskinesia, there were no apparent increases in depression or suicidal ideas either in the randomized portions of the clinical trials or in longer open-label extension periods (Solmi et al. 2018c). Nevertheless, occurrence of depression or suicidal ideas could occur during treatment for tardive dyskinesia and clinicians will want to be alert to this possibility.

Small clinical trials and case series have examined other treatments for tardive dyskinesia. Some benefits have been noted with benzodiazepines (Bergman et al. 2018a), although the potential for benefits must be weighed against the potential side effects of these medications including somnolence, cognitive difficulties, problems with coordination, and risk of misuse or development of a sedative use disorder. In high doses and particularly in combination with alcohol, other sedating medications, or opioids, respiratory depression may occur. A change in antipsychotic therapy to clozapine also seems to be associated with a reduction in tardive dyskinesia, particularly for individuals with moderate to severe symptoms (Mentzel et al. 2018). In general, giving a higher dose of an antipsychotic may suppress movements of tardive dyskinesia in the short-term but would be expected to escalate further development of tardive dyskinesia in the long-term. Nevertheless, there may be life threatening circumstances (e.g., patients with constant movement, gagging, or choking) where rapid suppression of dyskinesia is needed, and judicious use of an antipsychotic may be appropriate.

For individuals with other tardive syndromes, other approaches may be helpful on an individual basis. For example, depending on the muscle group that is affected, injections of botulinum toxin have been used to treat tardive dystonia (Brashear et al. 1998; Jinnah and Factor 2015). In addition, tardive dystonia may respond to beta-adrenergic blocking agents (Hatcher-Martin et al. 2016) and, in rare cases of severe intractable tardive dystonia, deep brain stimulation might be considered (Paschen and Deuschl 2018). High doses of anticholinergic agents have also been used to treat severe tardive dystonia, although these medications do not improve and may even worsen tardive dyskinesia (Bergman and Soares-Weiser 2018) in addition to producing significant side effects. Reserpine, which also depletes monoamines, should not be used to treat tardive syndromes as it has high rates of associated depression and suicidal ideas as well as lowering blood pressure (Micromedex 2019). Other treatments, such as vitamin B6 or vitamin E, are less likely to be associated with harms but do not appear to be associated with benefits in treating tardive dyskinesia (Adelufosi et al. 2015; Soares-Weiser et al. 2018a).
Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
In individuals with moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy, VMAT2 inhibitors can be associated with significant reductions in motor signs and symptoms of tardive dyskinesia. These medications may also be effective in other tardive syndromes.

Harms
The harms of treatment with VMAT2 inhibitors include sedation and, with tetrabenazine, extrapyramidal effects, akathisia, insomnia, anxiety, nausea, and falls. Depression and suicidal ideas have been reported in individuals who were administered VMAT2 inhibitors for treatment of Huntington's disease. Such effects are possible in individuals treated for tardive dyskinesia although they were not reported in clinical trials.

Patient Preferences
Clinical experience suggests that most patients with moderate to severe or disabling tardive dyskinesia wish to have a diminution of their motor signs and symptoms. Most patients would be willing to take medication to achieve a reduction in motor signs and symptoms, particularly if it was well tolerated.

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as far outweighing the potential harms. The majority of individuals with moderate to severe or disabling tardive dyskinesia would have a greater likelihood of experiencing benefits of a VMAT2 inhibitor than experiencing harms. Patient preferences to reduce motor signs and symptoms are also likely to favor treatment. (For additional discussion of the research evidence, see Appendix C, Statement 13.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations
The WFSBP guideline notes that tetrabenazine might have positive effects on tardive dyskinesia (Hasan et al. 2013). It also notes that the risk of tardive dyskinesia is less with SGAs than with FGAs and that there is limited evidence of benefit with clozapine for tardive dyskinesia. Information on a range of other treatments is noted to be even less conclusive. The practice guideline of the American Academy of Neurology, which was also published before the availability of deutetrabenazine and valbenazine, notes that tetrabenazine might be considered as a treatment for tardive syndromes (Bhidayasiri et al. 2013).

Quality Measurement Considerations
This statement alone is not sufficient in supporting the development of a quality measure due to the difficulty posed when defining "moderate to severe or disabling tardive dyskinesia" as a specification criterion. However, it may be possible to incorporate this recommendation into internal quality improvement initiatives focused on enhanced identification and treatment of tardive syndromes.
Psychosocial Interventions

Statement 14

APA recommends (1B) that patients with schizophrenia be treated with cognitive-behavioral therapy (CBT). *

Implementation

The use of CBT for individuals with schizophrenia has a number of potential benefits including improvements in quality of life and global, social, and occupational function, and reductions in core symptoms of illness, such as positive symptoms. However, it is important to appreciate that these benefits have been found in studies of CBT that is adapted to use for individuals with psychosis (CBTp), which has some differences from CBT that is focused on other indications. For example, with CBTp, the treatment is delivered in a more flexible fashion with less focus on setting a precise agenda. Rather than providing information on cognitive distortions and actively helping patients to challenge such thinking, CBTp takes a less structured empathic approach. More specifically, CBTp focuses on guiding patients to develop their own alternative explanations for maladaptive cognitive assumptions, which are healthier, realistic, and do not perpetuate the patient’s convictions regarding the veracity of delusional beliefs or hallucinatory experiences. Thus, the overall approach with CBTp includes developing a collaborative and nonjudgmental therapeutic relationship in which patients can learn to monitor relationships between thoughts, feelings, behaviors, and symptoms and evaluate the perceptions, beliefs, and thought processes that contribute to symptoms (Beck and Rector 2005; Beck et al. 2009; Beck Institute 2019; Hardy 2019; Kingdon and Turkington 2019; Landa 2019; Lecomte et al. 2016; Morrison 2017; Turkington et al. 2006; Wright et al. 2009). Through this dual focus on monitoring and evaluation, patients can develop beneficial coping strategies and improve functioning with behavioral self-monitoring serving as a basis for graded task assignments or activity scheduling. In addition, symptoms can be discussed as being within a range of normal experiences (e.g., hearing a loved one’s voice in the context of grief) and alternative explanations for symptoms can be developed that help reduce associated stress (Turkington et al. 2006).

CBTp can be started in any treatment setting, including inpatient settings, and during any phase of treatment (Turkington et al. 2006). It can also be conducted in group as well as in individual formats, either in-person or via web-based delivery platforms. Although patient preferences and treatment availability may influence choice of a delivery method, there do not appear to be clear-cut differences in the treatment benefits of group as compared to individual CBTp (McDonagh et al. 2017; Wykes et al. 2008). The duration of treatment with CBTp has varied in research and clinical practice with a range from 8 weeks to 5 years of treatment reported in the literature (McDonagh et al. 2017). However, guidelines from other countries recommend a minimum treatment duration of 16 sessions of CBTp (National Institute for Health and Care Excellence 2014; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2014; Scottish Intercollegiate Guidelines Network 2015).

* 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.

** Videos that demonstrate some of the approaches to CBTp are available at: I can feel better: https://www.icanfeelbetter.org/cbtpskills. Accessed on April 1, 2019.
Guidelines Network 2013). Although the available research suggests that treatment benefits are no longer significant when assessed more than 6 months after the end of a CBTp course (McDonagh et al. 2017), it is unclear whether longer durations of treatment with CBTp will result in greater benefits or will help in maintaining treatment-related improvements.

Issues with implementation of CBTp have also been examined. Although the methodological rigor of most studies has been low (Ince et al. 2016), common barriers to CBTp have been identified. For example, some individuals with schizophrenia may be too symptomatic or are experiencing too many side effects (e.g., sedation) to allow effective participation, particularly in inpatient settings. From a patient-centered perspective, CBTp was sometimes viewed as more emotionally challenging and requiring more effort (e.g., homework) than other psychological therapies (Wood et al. 2015). Attitudinal barriers of staff and organizational management were also found to be common and included a lack of understanding of CBTp and negative expectancies about its value. In addition to inadequate availability of trained staff, staff reported difficulty in identifying patients who were most likely to benefit from CBTp as well as a lack of dedicated time to provide CBTp. Insufficient initial training and insufficient reinforcement of training were also common. Thus, for CBTp to be effective, individuals who are providing CBTp should have appropriate training using established approaches and supervision in CBTp techniques. In addition, concerted efforts may be needed to foster positive attitudes and assure adequate time to deliver CBTp. At organizational or health system levels, attention to enhancing the availability of CBTp is also important given the limited availability of CBTp in the U.S.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
Use of CBTp in the treatment of schizophrenia can be associated with overall reductions in core illness symptoms, such as positive symptoms (moderate SOE). CBTp can also be associated with short-term improvements (e.g., for up to 6 months) in quality of life (low SOE) and global, social, and occupational function (moderate SOE).

Harms
The harms of CBTp in the treatment of schizophrenia are not well delineated or systematically studied but are likely to be small based on the small number of reported harms in clinical trials.

Patient Preferences
Clinical experience suggests that many patients are cooperative with and accepting of CBTp as part of a treatment plan; however, other patients may not wish to participate in CBTp, may be reluctant to adhere to assignments in between sessions, or may experience logistical barriers (e.g., time, transportation, childcare, costs) in attending CBTp sessions.

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as far outweighing the potential harms. Specifically, the potential for modest benefits in important patient-centered outcomes during and for periods of up to 6 months after CBTp treatment seemed to outweigh the minimal harms of CBTp treatment. (For additional discussion of the research evidence, see Appendix C, Statement 14.)
Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Statements from other practice guidelines are consistent with this recommendation. The RANZCP and NICE guidelines recommend the use of CBTp for all individuals with schizophrenia (Galletly et al. 2016; National Institute for Health and Care Excellence 2014) whereas the SIGN, CSG, and PORT guidelines recommend CBTp for individuals who have persistent symptoms despite treatment with an antipsychotic medication (Dixon et al. 2010; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013). The NICE, SIGN, and CSG guidelines note that CBTp should include at least 16 planned CBTp sessions (National Institute for Health and Care Excellence 2014; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations

This guideline statement is not appropriate for a performance-based quality measure because of the impact of patient preferences and logistical barriers to CBT including geographic variations in availability of CBT for psychosis. Reminders about CBT are also not well-suited to incorporation into electronic health record clinical decision support. However, anecdotal observations suggest that use of CBT for psychosis is infrequent in the U.S. Consequently, health organizations and health plans may wish to implement programs to increase the use of CBT among individuals with schizophrenia.

Statement 15

APA recommends (1B) that patients with schizophrenia receive psychoeducation.*

Implementation

Elements of psychoeducation are an integral part of good clinical practice. For example, APA's Practice Guideline on Psychiatric Evaluation emphasizes the importance of involving patients in treatment related decision-making and recommends providing the patient with education about the differential diagnosis, risks of untreated illness, treatment options, and benefits and risks of treatment (American Psychiatric Association 2016). However, these informal approaches to psychoeducation have been expanded into formal, systematically delivered programs of psychoeducation that have been evaluated through clinical trials (Pekkala and Merinder 2002).

The psychoeducational programs that have been studied have varied in their format, duration, and scope. Some psychoeducational programs are delivered on an individual basis whereas others are delivered in a group format, often in conjunction with family members or other individuals who are involved in the patient's life. In clinical trials, a 12-session program of psychoeducation is the norm; however, briefer psychoeducation programs of 10 sessions or less have also been studied (Pekkala and

* 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.
Typically, psychoeducation is conducted on an outpatient basis but elements of formal psychoeducation programs can also be incorporated into care in inpatient settings. Information that is commonly conveyed in a psychoeducation program includes key information about diagnosis, symptoms, psychosocial interventions, medications, and side effects as well as information about stress and coping, crisis plans, early warning signs, and suicide and relapse prevention (Bäuml et al. 2006). In addition to conveying empathy and respect for the individual, psychoeducation is delivered in a manner that aims to stimulate hope, reassurance, resilience, and empowerment. Typically, psychoeducation incorporates multiple educational modalities such as workbooks (McCrary et al. 2019), pamphlets, videos, and individual or group discussions in achieving the goals of psychoeducation. Barriers to providing psychoeducation as a part of the treatment plan primarily relate to program availability. On-line delivery of psychoeducation may be one approach to enhancing availability.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
Use of psychoeducation in the treatment of schizophrenia can be associated with a number of potential benefits including improvements in global function (low SOE) and reductions in relapse rates (moderate SOE). Enhancements in treatment adherence and improved satisfaction with mental health services have also been noted in some studies.

Harms
The harms of psychoeducation are likely to be minimal based on results from clinical trials that show no differences in the rate of harms experienced by individuals treated with psychoeducation as compared to usual care (low SOE).

Patient Preferences
Clinical experience suggests that most patients are interested in receiving information about their diagnosis and potential treatments as part of their care. In addition, most patients are accepting of more formal and systematic approaches to psychoeducation. However, some patients may not wish to participate in psychoeducation or may experience logistical barriers (e.g., time, transportation, childcare, costs) in attending psychoeducation sessions.

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as far outweighing the potential harms. Specifically, any minimal harms of psychoeducation seem to be outweighed by the potential for modest benefits in important patient-centered outcomes such as improvements in global function and reductions in relapse rates. (For additional discussion of the research evidence, see Appendix C, Statement 15.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.
Review of Available Guidelines from Other Organizations

Guidelines from other organizations including CSG, RANZCP, and SIGN, note the value of psychoeducation for individuals with schizophrenia including information about diagnosis (Galletly et al. 2016; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations

This guideline statement is not appropriate for a performance-based quality measure because of the impact of patient preferences and logistical barriers to psychoeducation. Reminders about psychoeducation are also not well-suited to incorporation into electronic health record clinical decision support. However, health organizations and health plans may wish to implement quality improvement efforts to increase the use of formal psychoeducational programs among individuals with schizophrenia.

Statement 16

APA recommends (1B) that patients with schizophrenia receive supported employment services.*

Implementation

Supported employment differs from other vocational rehabilitation services in providing assistance in searching for and maintaining competitive employment concurrently with job training, embedded job support, and mental health treatment (Frederick and VanderWeele 2019). In contrast, other vocational rehabilitation approaches focus on training before placement and greater emphasis on placement in sheltered and transitional employment rather than in a competitive employment setting (Marino and Dixon 2014).

Of approaches to supported employment, the bulk of studies involve individual placement and support (IPS) (Frederick and VanderWeele 2019; McDonagh et al. 2017). In addition to a focus on rapid attainment of competitive employment, IPS emphasizes patient preferences in the services that are delivered, the outreach that occurs with potential employers, and eligibility for the program (Marino and Dixon 2014). Additional principles of IPS include individualized, long-term job support and integration of employment specialists with the clinical team. Employment specialists also develop relationships with community employers and provide personalized benefits counseling to participants.

Evidence consistently shows that supported employment is associated with greater rates of competitive employment than transitional employment or pre-vocational training, although pre-vocational training is superior to no vocational intervention at all (Marshall et al. 2014; McDonagh et al. 2017; Metcalfe et al. 2018; Modini et al. 2016; Richter and Hoffmann 2018; Suijkerbuijk et al. 2017). Augmenting supported employment with symptom-related skills training, training in workplace fundamentals, or cognitive training may assist in gaining and maintaining competitive employment (Dewa et al. 2018; Suijkerbuijk et al. 2017). Other benefits of supportive employment include greater number of hours worked per week, a longer duration of each job, a longer duration of total employment, and an increase in earnings (McDonagh et al. 2017). Individuals receiving supported employment are also more likely to obtain job related accommodations than individuals with mental illness who are not receiving supported

* 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.
employment (McDowell and Fossey). Such accommodations typically relate to support from the supported employment coach but may also include flexible scheduling, reduced hours, modified job duties, and modified training and supervision.

Among individuals who receive supported employment, factors that may be associated with a greater likelihood of success include lower levels of symptoms, higher levels of cognitive functioning (e.g., attention, memory, executive functioning, psychomotor speed), greater work success in the past, higher levels of educational attainment, and greater interest in obtaining employment (Kirsh 2016). Peer support and support from families and others in the patient's social network may also be associated with better outcomes, although these factors have been less well studied (Kirsh 2016).

There are a number of barriers to supported employment, including economic and regulatory factors (Kirsh 2016; Metcalfe et al. 2018; Modini et al. 2016) and the limited number of available programs (Marshall et al. 2014; Sherman et al. 2013). Employers may be reluctant to participate in supported employment out of concern about the impact of providing work-related accommodations and because of discrimination and bias towards individuals with serious mental illness (Kirsh 2016). Treating clinicians may also serve as a barrier by having inappropriately limited expectations of the vocational capacities of individuals with schizophrenia (Kirsh 2016). In addition, concerns about losing disability benefits or health insurance may lead some individuals to forego supported employment opportunities (Kirsh 2016). Within supported employment programs, organizational barriers to success have included poor fidelity to supported employment principles (Marshall et al. 2014); insufficient time devoted to leading and management of the programs; and insufficient training, skills, and business and public relations knowledge of program staff (Kirsh 2016; Swanson et al. 2013). Each of these barriers are important to address at individual, systems, and policy levels so that more patients can benefit from supported employment interventions.

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Use of supported employment as part of the treatment of schizophrenia can be associated with significantly better employment outcomes including a significantly greater likelihood of obtaining competitive employment (moderate SOE), a significantly greater likelihood of working more than 20 hours per week, more weeks of employment, and greater earnings relative to vocational training or no vocational interventions.

**Harms**

The harms of supported employment in the treatment of schizophrenia are not well delineated or systematically reported but are likely to be small.

**Patient Preferences**

Clinical experience suggests that few patients are currently receiving supported employment but that a significant number of individuals may be interested in supported employment if it were readily available.
and offered to them. However, some individuals may be in school, have responsibilities at home, or already be employed. Others would rather not seek employment or may have concerns about losses of benefits or health insurance if they did pursue competitive employment. Logistical barriers (e.g., transportation, childcare) may also affect patient preferences related to supported employment.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. Specifically, the potential for benefits in important patient-centered outcomes related to employment seemed to outweigh the minimal harms of supported employment programs. (For additional discussion of the research evidence, see Appendix C, Statement 16.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

Guidelines from other organizations are generally consistent with this recommendation. NICE and PORT recommend that supported employment be offered to individuals with schizophrenia who wish to find or return to work (Dixon et al. 2010; National Institute for Health and Care Excellence 2014) and RANZCP recommends IPS services for individuals with first episode psychosis (Galletly et al. 2016). RANZCP, NICE, and CSG also emphasize the appropriateness of other occupational or educational activities for individuals with schizophrenia (Galletly et al. 2016; National Institute for Health and Care Excellence 2014; Norman et al. 2017).

Quality Measurement Considerations

This guideline statement is not appropriate for a performance-based quality measure because of the impact of patient preferences and barriers to supported employment including variations in availability. Reminders about supported employment are also not well-suited to incorporation into electronic health record clinical decision support. However, given the infrequent availability of supported employment in the U.S., health organizations and health plans may wish to implement programs to increase the use of supported employment among individuals with schizophrenia.

Statement 17

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).*

Implementation

Assertive community treatment (ACT), sometimes referred to as programs of assertive community treatment, is a multidisciplinary, team-based approach in which patients receive individualized care outside of a formal clinical setting. Thus, individuals may be engaged in their homes, workplaces, or other community locations. Continuity of care is enhanced because individuals work with an assigned

* 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.
team, which has 24/7 availability, rather than being assigned to a designated clinician for care. Team members typically include a psychiatrist, nurse, and social worker or case manager. Peer specialists, vocational specialists, and clinicians with expertise in substance use treatment are often part of the team as well. Other features of ACT include its flexibility to provide personalized and flexible care that addresses the patient's needs and preferences without time-limits or other constraints on services. ACT teams also work with a smaller number of individuals than traditional outpatient clinicians or case managers, which contributes to the ability to provide frequent visits and a more personalized and comprehensive approach to care. Particularly in rural areas, some ACT teams are augmenting face-to-face visits with telepsychiatry visits, although research will be needed to determine whether such an approach alters the benefits of ACT (Swanson and Trestman 2018).

Studies of ACT suggest that it is associated with comparable symptom improvement to other treatment delivery approaches, but that individuals who receive ACT are more likely to be domiciled, living independently, working, and less likely to be hospitalized as compared to individuals who receive treatment as usual (McDonagh et al. 2017). Although ACT has multiple strengths that would make it an attractive approach in individuals with co-occurring disorders and schizophrenia, the impact of ACT on physical health has not been well studied (Vanderlip et al. 2017). Also, in individuals with a concomitant substance use disorder, research to date has not shown associated improvements in functioning, mortality, or substance use as compared to usual care (McDonagh et al. 2017).

In terms of implementation barriers, there is often limited availability of ACT programs. Funding of programs can be challenging because the comprehensive and multidisciplinary nature of ACT services are not well aligned with payment models in the U.S. health care delivery system (Monroe-DeVita et al. 2012). Effective delivery of ACT services is also dependent upon having high-fidelity to ACT program standards (Monroe-DeVita et al. 2012; Thorning et al. 2016) and this requires considerable training as well as ongoing mentoring, learning collaboration, and consultation with individuals who are skilled in ACT implementation. Attention to outcomes and organizational culture are also important in providing a team-based approach that is warm, flexible, pragmatic, collaborative, and supportive of patients' recovery (Monroe-DeVita et al. 2012). For organizations or state mental health systems that are implementing ACT programs, a number of resources are available (Case Western Reserve University 2019; Substance Abuse and Mental Health Services Administration 2008; Thorning et al. 2016).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits
Use of ACT in the treatment of schizophrenia can be associated with a number of benefits as compared to treatment as usual including a greater likelihood of being domiciled, living independently, or working, and a lower likelihood of being hospitalized (low to moderate SOE).

Harms
The harms of ACT in the treatment of schizophrenia are not well delineated but are likely to be small.
Patient Preferences

Clinical experience suggests that most patients are cooperative with and accepting of ACT, particularly once they have engaged with treatment. In some circumstances, ACT is used as one component of court-mandated care (e.g., assisted outpatient treatment, community treatment order, outpatient commitment) and patients may be reluctant to accept ACT in this context. However, in the few studies that have examined patient perceptions, ACT is generally viewed as supporting patients and building relationships in a recovery-oriented fashion (Appelbaum and Le Melle 2008; Morse et al. 2016).

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms. ACT is generally viewed positively by patients and it improves a number of patient-oriented outcomes with minimal risk of harms. (For additional discussion of the research evidence, see Appendix C, Statement 17.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

Review of Available Guidelines from Other Organizations

This guideline recommendation is consistent with the SIGN recommendation to offer assertive outreach to individuals with schizophrenia who "make high use of inpatient services, who show residual psychotic symptoms and who have a history of poor engagement with services leading to frequent relapse and/or social breakdown (for example homelessness)" (Scottish Intercollegiate Guidelines Network 2013). The PORT guideline also notes that ACT should be included in systems of care that serve individuals with schizophrenia and that it "should be provided to individuals who are at risk for repeated hospitalizations or have recent homelessness" (Dixon et al. 2010). In addition, RANZCP recommends the use of ACT "after initial contact, during crises and after discharge from hospital" in individuals with schizophrenia (Galletly et al. 2016).

Quality Measurement Considerations

This guideline statement is not appropriate for a performance-based quality measure because of the impact of patient preferences and logistical barriers to ACT including geographic variations in availability. Reminders about ACT are also not well-suited to incorporation into electronic health record clinical decision support. However, anecdotal observations suggest that more patients may benefit from ACT in the U.S. than currently receive it. Consequently, state mental health agencies, health plans, and health organizations may wish to implement programs to increase the use of ACT among individuals with schizophrenia who have had a history of poor engagement with services leading to frequent relapse or social disruption (e.g., homelessness; legal difficulties, including imprisonment).

Statement 18
APA recommends (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a team-based, multicomponent program. *

Implementation

For individuals with a first episode of psychosis, team-based, multicomponent treatment programs have been developed that integrate a number of evidence-based interventions into a comprehensive treatment package. For example, the NAVIGATE program, which was developed for the Recovery After an Initial Schizophrenia Episode (RAISE) - Early Treatment Program, uses a collaborative, shared decision-making approach that incorporates family involvement and education, individual resiliency training, supported employment and education, and individualized medication treatment (Mueser et al. 2015). Similar team-based, multicomponent interventions have been used in other countries for treatment of early psychosis (Anderson et al. 2018; Craig et al. 2004; Secher et al. 2015). These treatment programs have been associated with a number of benefits including lower mortality (Anderson et al. 2018), lower rates of relapse, better quality of life, better global function, and greater likelihood of working or being in school after receiving up to two years of treatment (McDonagh et al. 2017). Patients in such programs may also experience a greater sense of empowerment and support for their autonomy (Browne et al. 2017).

The main barriers to implementing this recommendation in practice relates to the limited availability of first-episode, multicomponent treatment programs. For state health agencies, health systems, or organizations that are implementing such programs, barriers include issues such as funding, training, and implementation support. However, consultation and implementation materials are available to help guide the establishment of new programs and ensure program fidelity with evidence-based approaches (National Institute of Mental Health 2019; OnTrackNY 2019; RAISE Early Treatment Program 2019).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

Use of a team-based, multicomponent treatment program for individuals with a first episode of psychosis can be associated with lower mortality, lower rates of relapse, better quality of life, better global function, and greater likelihood of working or being in school after receiving up to two years of treatment (low to moderate SOE)

Harms

The harms of a team-based, multicomponent treatment program for individuals with a first episode of psychosis are not well delineated but are likely to be small.

Patient Preferences

Clinical experience suggests that many patients with a first episode of psychosis are cooperative with and accepting of a team-based, multicomponent treatment program; however, other patients may not wish to take part in such a program out of a belief that they do not have a condition that requires

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treatment or because of logistical barriers that influence their ability to access the more intensive
treatment provided by such a program.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms.
Team-based, multicomponent treatment is generally viewed positively by patients and it improves a
number of patient-oriented outcomes with minimal risk of harms. (For additional discussion of the
research evidence, see Appendix C, Statement 18.)

Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this
recommendation.

Review of Available Guidelines from Other Organizations

Other guidelines did not specifically address the use of team-based, multicomponent treatment
programs, but they do endorse many of the individual elements of such programs (e.g., family
engagement, psychoeducation, supported employment, medication treatment).

Quality Measurement Considerations

This guideline statement is not appropriate for a performance-based quality measure because of the
impact of patient preferences and geographic variations in the availability of team-based,
multicomponent treatment. Reminders about team-based, multicomponent treatment are also not
well-suited to incorporation into electronic health record clinical decision support. However, more
patients may benefit from team-based, multicomponent treatment in the U.S. than currently receive it.
Consequently, state mental health agencies, health plans, and health organizations may wish to
implement programs to increase the use of team-based, multicomponent treatment among individuals
with a first episode of psychosis.

Statement 19

APA suggests (2C) that patients with schizophrenia receive cognitive remediation.*

Implementation

Cognitive remediation approaches are intended to address cognitive difficulties that can accompany
schizophrenia with the aim of enhancing function and quality of life. A number of different cognitive
remediation approaches have been used, typically in group or computer-based formats, in an effort to
enhance cognitive processes such as attention, memory, executive function, social cognition, or meta-
cognition (Delahunty and Morice 1996; Medalia et al. 2018; Reeder et al. 2016; Wykes et al. 2011).
Some programs have focused on improving cognitive flexibility (e.g., shifting cognitive sets), working
memory (e.g., sequencing, multi-tasking, delayed recall), and planning (e.g., active coding; sequencing
and chunking), whereas meta-cognitive approaches have attempted to teach patients how and when

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includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.
particular strategies can be used that bypass specific cognitive limitations. Some programs add aspects of social and communication skills to neurocognitive elements of remediation (Pentaraki et al. 2017).

Although this variability in program format and content confounds interpretation of the evidence, cognitive remediation does seem to result in improvements in cognition, symptoms, and function at least on a short-term basis (Harvey et al. 2018; McDonagh et al. 2017; Revell et al. 2015). However, some apparent improvements in cognitive performance may result from practicing specific tasks and may not produce generalizable changes in other contexts. Furthermore, the specific elements of a particular cognitive remediation program may influence the benefits that are observed (Cella and Wykes 2019).

The primary barriers to use of cognition remediation are related to program availability. Use of on-line delivery of cognitive remediation may be one way to overcome these barriers. Information and training on developing cognitive remediation programs are available (Medalia 2019; Medalia et al. 2018).

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Use of cognitive remediation is associated with small improvements in specific aspects of cognition (Harvey et al. 2018) as well as small positive effects on social, occupational, and global function, core illness symptoms (low SOE), and negative symptoms (moderate SOE) compared with usual care over approximately 16 weeks of treatment (McDonagh et al. 2017).

**Harms**

The harms of cognitive remediation in the treatment of schizophrenia are not well-studied but are likely to be small.

**Patient Preferences**

Evidence from research trials suggests that patients are likely to be cooperative with and accepting of cognitive remediation as part of a treatment plan (Reeder et al. 2016); however, other patients may not wish to participate due to logistical barriers (e.g., time, cost, transportation, childcare).

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms, which were viewed as minimal. Differences in patient preferences, variability in the appropriateness of cognitive remediation for individuals with schizophrenia, and the unclear durability of benefits led to suggesting cognitive remediation rather than recommending it. (For additional discussion of the research evidence, see Appendix C, Statement 19.)

**Differences of Opinion Among Writing Group Members**

There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

**Review of Available Guidelines from Other Organizations**

The RANZCP guideline recommends that cognitive remediation be available to individuals with schizophrenia if cognitive impairment is present and should be specifically "offered when cognitive
deficits are affecting recovery and function” (Galletly et al. 2016). The SIGN and CSG guidelines note that cognitive remediation “may be considered for individuals diagnosed with schizophrenia who have persisting problems associated with cognitive difficulties” (Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013).

Quality Measurement Considerations
As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure or incorporation into electronic decision support.

Statement 20
APA suggests (2C) that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*

Implementation
Illness self-management training programs have been applied to help address many chronic conditions and are designed to improve knowledge about one's illness and management of symptoms (Grady and Gough 2014). Goals include reducing the risk of relapse, recognizing signs of relapse, developing a relapse prevention plan, and enhancing coping skills to address persistent symptoms with the aims of improving quality of life and social and occupational functioning. In the studies included in the AHRQ review, self-management training was generally delivered in a group setting with sessions of 45 minutes to 90 minutes each and the number of intervention sessions ranged from 7 to 48 sessions (McDonagh et al. 2017). However, the evidence suggested better outcomes in patients who participated in at least 10 self-management intervention sessions. Self-management sessions were typically facilitated by clinicians although peer-facilitated sessions have also been used. In addition, some studies have used individually targeted interventions, either face-to-face or via computer-based formats (Lean et al. 2019). Self-management approaches have also been used to address co-occurring medical conditions in individuals with serious mental illness including schizophrenia with benefits that included increased patient activation and improved health-related quality of life (Druss et al. 2018; Goldberg et al. 2013; Muralidharan et al. 2019).

Recovery-focused interventions have also been developed that focus on fostering self-determination in relation to a patient's personal goals, needs, and strengths. Such approaches may include elements of self-management skill development and psychoeducation but also include components and activities that allow participants to share experiences and receive support, learn and practice strategies for success, and identify and take steps toward reaching personal goals. Studies of recovery-focused interventions have been smaller in number but suggest that these interventions can promote increased recovery, hope, and empowerment among individuals with serious mental illnesses (Le Boutillier ET AL. 2011; Thomas et al. 2018).

The most common barrier to implementing this guideline statement is the availability of programs for developing self-management skills and enhancing person-oriented recovery. However, a toolkit for

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* 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.
developing illness management and recovery-based programs in mental health is available through the Substance Abuse and Mental Health Services Administration (Substance Abuse and Mental Health Services Administration 2010).

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Use of interventions aimed at developing self-management skills and enhancing person-oriented recovery in individuals with schizophrenia can be associated with reductions in symptom severity and risk of relapse and an increased sense of hope and empowerment (low to moderate SOE). Self-management approaches that are aimed at addressing co-occurring medical conditions in individuals with serious mental illness also have benefits that include increased patient activation and improved health-related quality of life.

**Harms**

The harms of interventions aimed at developing self-management skills and enhancing person-oriented recovery in the treatment of schizophrenia are not well studied but are likely to be minimal.

**Patient Preferences**

Clinical experience suggests that most patients are cooperative with and accepting of interventions aimed at developing self-management skills and enhancing person-oriented recovery. However, some patients may not wish to take part in such interventions due to personal preferences or logistical barriers (e.g., transportation, childcare) to attending group sessions.

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement in terms of patient engagement, empowerment, and beneficial outcomes were viewed as likely to outweigh the potential harms, which were viewed as minimal. (For additional discussion of the research evidence, see Appendix C, Statement 20.)

**Differences of Opinion Among Writing Group Members**

There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

**Review of Available Guidelines from Other Organizations**

This guideline statement is consistent with recommendations of other guidelines (RANZCP, NICE) that support the use of self-management and peer-support programs in the treatment of individuals with schizophrenia (Galletly et al. 2016; National Institute for Health and Care Excellence 2014).

**Quality Measurement Considerations**

As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure or incorporation into electronic decision support. Nevertheless, health care organizations and health plans may wish to track the availability and utilization of programs to develop self-management skills and enhance person-oriented recovery given the potential benefits of such interventions.

**Statement 21**
APA suggests (2C) that patients with schizophrenia be treated with supportive psychotherapy.*

Implementation

Supportive psychotherapy is commonly a part of the treatment plan in individuals with schizophrenia who are not receiving other modes of psychotherapy (e.g., CBTp) although the evidence related to its benefits is limited. When compared to treatment as usual, no advantage was seen for psychotherapy in terms of global or social function (Buckley et al. 2015; McDonagh et al. 2017); however, these finding are difficult to interpret given the frequent use of supportive psychotherapy techniques as part of usual care. When compared to insight-oriented psychotherapies, a small number of early studies suggested that supportive psychotherapy might be associated with better outcomes in coping skills, adherence, and relapse (Fenton 2000; Hogarty et al. 1997; Stanton et al. 1984).

The focus of supportive psychotherapy is reality-based and present-centered (Kates and Rockland 1994; Novalis et al. 1993; Winston 2014; Winston et al. 2012). It commonly aims to help patients cope with symptoms, improve adaptive skills, and enhance self-esteem, although descriptions of the goals of supportive psychotherapy have varied. Examples of techniques used to foster these goals include reassurance, praise, encouragement, explanation, clarification, reframing, guidance, suggestion, and use of a conversational, non-confrontational style of communication. Many of the common elements that have been identified in effective psychotherapies, including a positive therapeutic alliance, are also integral to supportive psychotherapy (Frank and Frank 1991; Wampold 2015). Typically, supportive psychotherapy is conducted in conjunction with medication management at a frequency that can vary from weekly to every few months depending on the needs of the individual patient. Other psychosocial treatments can also be used as part of the treatment plan in conjunction with these modalities.

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

Use of supportive psychotherapy in the treatment of schizophrenia was not associated with relative benefits in global or social function as compared to treatment as usual (low SOE). However, treatment as usual already incorporates supportive psychotherapy under most circumstances. In addition, clinical experience suggests that supportive psychotherapy may be associated with benefits such as strengthening the therapeutic alliance, reducing demoralization, and developing practical coping strategies in the treatment of individuals with schizophrenia.

Harms

The harms of using supportive psychotherapy in the treatment of schizophrenia appear to be small though evidence is limited. However, if supportive psychotherapy is used preferentially instead of a treatment that is associated with more robust evidence of benefit, there may be indirect negative effects.

* 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.
Patient Preferences
Clinical experience suggests that most patients are cooperative with and accepting of supportive psychotherapy as part of a treatment plan, even when they are reluctant to engage in other psychosocial interventions. However, some patients may not wish to engage in psychotherapy or may have logistical barriers (e.g., time, transportation, financial considerations) that make it difficult to attend psychotherapy sessions.

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. In clinical practice, the use of supportive psychotherapy is commonplace as part of the treatment of schizophrenia, which makes it challenging to interpret the research comparisons of supportive psychotherapy versus treatment as usual. Given the limited evidence of any harms of supportive psychotherapy, the potential benefits of supportive psychotherapy appear to be greater than the harms. (For additional discussion of the research evidence, see Appendix C, Statement 21.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

Review of Available Guidelines from Other Organizations
The NICE guideline notes that supportive psychotherapy should not be offered routinely to individuals with schizophrenia if other psychosocial treatments are available that have greater efficacy (National Institute for Health and Care Excellence 2014). However, the NICE guideline also notes that patient preferences should be taken into account, particularly if other psychosocial intervention are not available locally.

Quality Measurement Considerations
As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure or incorporation into electronic decision support.

Statement 22
APA suggests (2B) that patients with schizophrenia who have ongoing contact with family receive family interventions.*

Implementation
An important aspect of good psychiatric treatment is involvement of family members and other individuals who play a key role in the patient's life. In addition to spouses, parents, children or other biological or non-biological relatives, such individuals may include people who reside with the patient, intimate partners, or close friends who are an integral part of the patient's support network. Such individuals benefit from discussion of topics such as diagnosis and management of schizophrenia, types of support that are available, and ways to access help in a crisis. Although some health professionals may be unsure about legal or regulatory aspects of sharing information, general information that is not

* 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.
specific to the patient can be provided (e.g., common approaches to treatment, general information about medications and their side effects, available support and emergency assistance). Most patients are accepting of family involvement. Nevertheless, even when a patient does not want a specific person to be involved in their care, the clinician may listen to information provided by that individual, as long as confidential information is not provided to the informant (American Psychiatric Association 2016). Also, to prevent or lessen a serious and imminent threat to the health or safety of the patient or others, the Principles of Medical Ethics (American Psychiatric Association 2013f) and the Health Insurance Portability and Accountability Act (HIPAA) (United States Department of Health and Human Services; Office for Civil Rights 2017a, 2017b) permit clinicians to disclose necessary information about a patient to family members, caregivers, law enforcement, or other persons involved with the patient. HIPAA also permits health care providers to disclose necessary information to the patient’s family, friends, or other persons involved in the patient’s care or payment for care when such disclosure is judged to be in the best interests of the patient and the patient is not present or is unable to agree or object to a disclosure due to incapacity or emergency circumstances (United States Department of Health and Human Services; Office for Civil Rights 2017b).

The family interventions that are suggested in this guideline statement go beyond the basics of family involvement that are important for good clinical care. These systematically delivered family interventions include illness education, crisis intervention, emotional support, and training in how to cope with illness symptoms and related problems (McDonagh et al. 2017; McFarlane 2016). The family interventions that have been studied include a variety of formats and approaches (McDonagh et al. 2017; McFarlane 2016). For example, some interventions occur in multi-family groups whereas others involve a single family and some interventions include the patient as part of the group whereas others do not. In terms of approach, some family interventions focus on psychoeducation whereas other interventions incorporate other treatment elements (e.g., motivational interviewing, goal setting, cognitive behavioral intervention, behavioral family therapy, support groups, social network development, communication training, role playing, stress management, relaxation training). Consequently, the selection of a specific family intervention should consider the preferences of the patient and family in collaboration with the clinician.

Benefits of family interventions include reductions in core symptoms of illness and reductions in relapses, including rehospitalization (McDonagh et al. 2017). Some studies have also shown benefits for family members such as reductions in levels of burden and distress or improvements in relationships among family members (McFarlane 2016; Sin et al. 2017). Evidence suggests that benefits of family interventions are greatest when more than 10 treatment sessions are delivered over a period of at least 7 months (McDonagh et al. 2017). However, the Family-to-Family Intervention available through the National Alliance on Mental Illness has shown significant benefits using a 12-week program consisting of weekly sessions of 2 to 3 hours each (Dixon et al. 2011; Lucksted et al. 2013; Marcus et al. 2013; Toohey et al. 2016).

A common barrier to implementing family interventions relates to program availability. However, the National Alliance on Mental Illness has reduced this barrier through its Family-to-Family program, which has led to a significant expansion in the availability of family interventions (National Alliance on Mental
Illness 2019). Additional barriers include constraints of family members (e.g., work schedules, transportation, childcare, health issues) that may limit their ability to be involved in frequent family sessions. Similar logistical barriers can exist for patients when family interventions incorporate patient participation. Other implementation barriers include organizational and clinician-focused barriers including time and cost constraints and insufficient understanding of the potential benefits of family intervention (Ince et al. 2016).

**Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement**

**Benefits**

Use of family interventions in the treatment of schizophrenia can reduce the likelihood of relapse (low to moderate SOE) and reduce core illness symptoms (low SOE).

**Harms**

The harms of family interventions in the treatment of schizophrenia are not well documented but appear to be minimal.

**Patient Preferences**

Clinical experience suggests that many patients are cooperative with and accepting of family interventions as part of a treatment plan; however, other patients may have had difficulties in relationships with family members in the past and may not want family members to be involved in their treatment.

**Balancing of Benefits and Harms**

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. For patients who have ongoing contact with their families, including relatives and significant others, there are distinct benefits to family interventions. However, some patients may not be in favor of family involvement even when they do have some ongoing contact with family members and, for this reason, the statement was suggested rather than being recommended for all individuals. (For additional discussion of the research evidence, see Appendix C, Statement 22.)

**Differences of Opinion Among Writing Group Members**

Eight writing group members voted in favor of this suggestion. One writing group member disagreed with this statement as worded feeling that it would be preferable for the guideline statement to make specific mention of others who may be involved with the patient in addition to family members.

**Review of Available Guidelines from Other Organizations**

This guideline statement is consistent with guidelines from other organizations. CGS, NICE, RANZCP, SIGN, and PORT guidelines all recommend offering family interventions when an individual with schizophrenia resides with or is in close contact with families (Dixon et al. 2010; Galletly et al. 2016; National Institute for Health and Care Excellence 2014; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013). These guidelines also emphasize the importance of providing information to family and others involved in the patient’s care on topics such as diagnosis and management of schizophrenia, types of support that are available, and ways to access help in a crisis.
Quality Measurement Considerations

As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure or incorporation into electronic decision support. Nevertheless, health care organizations and health plans may wish to track the availability and utilization of family interventions given the potential benefits of this approach.

Statement 23

APA suggests (2C) that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*

Implementation

Use of social skills training in the treatment of schizophrenia can improve social function, core illness symptoms, and negative symptoms more than usual care (McDonagh et al. 2017). Reductions in relapse rates, including rehospitalization rates, have also been noted in some studies (McDonagh et al. 2017).

Social skills training has an overarching goal of improving interpersonal and social skills but can be delivered using a number of approaches (Almerie et al. 2015; Kopelowicz et al. 2006; Turner et al. 2018). These include cognitive-behavioral, social-cognitive, interpersonal, and functional adaptive skills training. Social skills training is delivered in a group format and specific elements of the intervention will vary with the theoretical emphasis of the training. However, examples of techniques that can be used in social skills training include role playing, modeling, and feedback approaches to enhance interpersonal interactions; behaviorally-oriented exercises in assertiveness, appropriate contextual responses, and verbal and non-verbal communication; and instruction and practice with social and emotional perceptions (Almerie et al. 2015; Kopelowicz et al. 2006; Turner et al. 2018). These techniques are aimed at generating improvements in typical social behaviors such as making eye contact, smiling at appropriate times, actively listening to others, and sustaining conversations. In some social skills training programs, homework assignments, video, or technologically-based interventions are used to augment group sessions.

As with other psychosocial interventions, availability of social skills training is a common barrier to its incorporation into treatment. However, information about social skills training is available for organizations that wish to develop such programs (Bellak and Goldberg 2019; Bellak et al. 2004; Granholm et al. 2016).

Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement

Benefits

Use of social skills training in the treatment of schizophrenia can improve social function, core illness symptoms, and negative symptoms more than usual care (low SOE).

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* 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.
Harms
The harms of social skills training in the treatment of schizophrenia have not been well documented but appear to be minimal.

Patient Preferences
Clinical experience suggests that many patients are cooperative with and accepting of social skills training as part of a treatment plan; however, other patients may not wish to take part in social skills training due to logistical barriers (e.g., time, cost, transportation, child care) or having goals for treatment that are unrelated to social skills.

Balancing of Benefits and Harms
The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. Although the harms appear to be minimal, there is a low SOE for benefits and patient preferences may differ in terms of desiring to focus on social skills as a part of treatment. Consequently, this guideline statement was rated as a suggestion. (For additional discussion of the research evidence, see Appendix C, Statement 23.)

Differences of Opinion Among Writing Group Members
There were no differences of opinion. The writing group voted unanimously in favor of this suggestion.

Review of Available Guidelines from Other Organizations
Other guidelines are generally consistent with this guideline statement. The PORT, RANZCP, CSG, and SIGN guidelines suggest offering social skills training to individuals with schizophrenia who have deficits in social skills (Buchanan et al. 2010; Galletly et al. 2016; Norman et al. 2017; Scottish Intercollegiate Guidelines Network 2013). However, the NICE guideline notes that social skills training should not be routinely offered to individuals with schizophrenia (National Institute for Health and Care Excellence 2014).

Quality Measurement Considerations
As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure or incorporation into electronic decision support. Nevertheless, health care organizations and health plans may wish to track the availability and utilization of social skills training for individuals with schizophrenia given the potential benefits of such an approach for some patients.
Areas for Further Research

Overall:

• Improve generalizability of study populations
• Enhance study recruitment approaches and use a priori specification of subgroup analyses to obtain data on treatment effects in inpatients, minority groups, women, older individuals, individuals with multiple psychiatric or physical health conditions, and individuals with severe and/or treatment-resistant illness
• Assure that sample sizes are adequate to achieve statistical power
• Assure that studies report data in a consistent fashion and pre-specify outcomes of interest
• Assure that studies identify the magnitude of change in scale scores that constitutes a clinically meaningful difference
• With all treatments, more research is needed on approaches that improve patient-centered outcomes (e.g., quality of life, social functioning, physical health, recovery)
• With all treatments, but particularly with psychosocial interventions, systematic collection of information on harms is needed
• Optimizing treatment selection including pharmacogenomics and effects of demographic or sociocultural factors on treatment outcomes
• Long-term studies (at least one year with three-five year follow-up assessments) to determine durability of effects and development of long-term harms
• Use, benefits, and harms of treatments in individuals with co-occurring disorders (e.g., stimulants in co-occurring ADHD, benzodiazepines with co-occurring anxiety, smoking cessation interventions including medication and non-medication approaches with co-occurring nicotine dependence)

Medications and other somatic interventions

• Comparative effectiveness studies of newer SGAs (including LAIs, comparisons with some FGAs and use of comparable dosing strategies)
• Risks and benefits of strategies to minimize or treat side effects of antipsychotic medications, including use of concomitant medications, reductions in antipsychotic dose, or changing to a different antipsychotic medication
• Research on optimizing medication changes (i.e., switching from one antipsychotic to another)
• Research on neurostimulation approaches (e.g., ECT, TMS)

Psychosocial interventions

• Assure that psychosocial interventions are clearly defined and described and that measurements of fidelity to the intervention model are incorporated into the study design
• Research on optimizing long-term outcomes with psychosocial interventions (e.g., use of booster treatment sessions or continued treatment at a lower frequency for maintenance of therapeutic benefits in those with a good initial response)
Develop approaches to reduce the heterogeneity in "usual care" groups, which makes it difficult to interpret and compare studies of psychosocial interventions that use "usual care" as a control comparison.

Assure that studies of psychosocial interventions determine the intensity, frequency, and duration of treatment that is needed to optimize outcomes.

Guideline Development Process

This guideline was developed using a process intended to meet standards of the Institute of Medicine (2011) (now known as the National Academy of Medicine). The process is fully described in a document available on the APA Web site at: www.psychiatry.org/psychiatrists/practice/clinicalpractice-guidelines/guideline-development-process.

Management of Potential Conflicts of Interest

Members of the Guideline Writing Group (GWG) are required to disclose all potential conflicts of interest before appointment, before and during guideline development, and on publication. If any potential conflicts are found or disclosed during the guideline development process, the member must recuse himself or herself from any related discussion and voting on a related recommendation. The members of both the GWG and the Systematic Review Group (SRG) reported no conflicts of interest. The Disclosures section includes more detailed disclosure information for each GWG and SRG member involved in the guideline’s development.

Guideline Writing Group Composition

The GWG was initially composed of eight psychiatrists with general research and clinical expertise and a psychiatric resident (A.D.). This non-topic-specific group was intended to provide diverse and balanced views on the guideline topic to minimize potential bias. One psychiatrist (P.B.) and one psychologist (M.L.) were added to provide subject matter expertise in schizophrenia. An additional member (A.S.Y.) provided input on quality measure considerations. The vice-chair of the GWG (L.J.F.) provided methodological expertise on such topics as appraising the strength of research evidence. The GWG was also diverse and balanced with respect to other characteristics, such as geographical location and demographic background. <<ORG. NAME>> reviewed the draft and provided perspective from patients, families, and other care partners.

Systematic Review Methodology

The AHRQ’s systematic review, Treatments for Schizophrenia in Adults (McDonagh et al. 2017), served as the predominant source of information for this guideline. APA also conducted a search of additional systematic reviews and meta-analyses to include consideration of placebo-controlled trials that were not part of the AHRQ review.

An additional search was conducted in MEDLINE (PubMed) and PsycInfo on treatments for neurological side effects of antipsychotic medications including acute dystonia, parkinsonism, akathisia, and tardive syndromes. The search terms, limits used, and dates of these searches are available in Appendix B.
Results were limited to English-language, adult (18 and older), and human-only studies. These titles and abstracts were reviewed for relevance by one individual (L.J.F.).

Available guidelines from other organizations were also reviewed (Addington et al. 2017a, 2017b; Barnes et al. 2011; Buchanan et al. 2010; Crockford and Addington 2017; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Pringsheim et al. 2017; Scottish Intercollegiate Guidelines Network 2013).

Rating the Strength of Supporting Research Evidence

Strength of supporting research evidence describes the level of confidence that findings from scientific observation and testing of an effect of an intervention reflect the true effect. Confidence is enhanced by such factors as rigorous study design and minimal potential for study bias.

Ratings were determined, in accordance with the AHRQ’s Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Agency for Healthcare Research and Quality 2014), by the methodologist (L.J.F.) and reviewed by members of the SRG and GWG. Available clinical trials were assessed across four primary domains: risk of bias, consistency of findings across studies, directness of the effect on a specific health outcome, and precision of the estimate of effect.

The ratings are defined as follows:

- High (denoted by the letter A)=High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate (denoted by the letter B)=Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low (denoted by the letter C)=Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

The AHRQ has an additional category of insufficient for evidence that is unavailable or does not permit estimation of an effect. The APA uses the low rating when evidence is insufficient because there is low confidence in the conclusion and further research, if conducted, would likely change the estimated effect or confidence in the estimated effect.

Rating the Strength of Guideline Statements

Each guideline statement is separately rated to indicate strength of recommendation and strength of supporting research evidence. Strength of recommendation describes the level of confidence that potential benefits of an intervention outweigh potential harms. 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. As described in the section “Rating the Strength of Supporting Research Evidence”), this rating is a consensus judgment of the authors of the guideline and is endorsed by the APA Board of Trustees.
There are two possible ratings: recommendation or suggestion. 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 either 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. These strengths of recommendation correspond to ratings of strong or weak (also termed conditional) as defined under the GRADE method for rating recommendations in clinical practice guidelines (described in publications such as Guyatt et al. 2008 and others available on the Web site of the GRADE Working Group at http://www.gradeworkinggroup.org/).

When a negative statement is made, ratings of strength of recommendation should be understood as meaning the inverse of the above (e.g., recommendation indicates confidence that harms clearly outweigh benefits). The GWG determined ratings of strength of recommendation by a modified Delphi method using blind, iterative voting and discussion. In order for the GWG members to be able to ask for clarifications about the evidence, the wording of statements, or the process, the vice-chair of the GWG served as a resource and did not vote on statements. All other formally appointed GWG members, including the chair, voted.

In weighing potential benefits and harms, GWG members considered the strength of supporting research evidence, their own clinical experiences and opinions, and patient preferences. For recommendations, at least 10 out of 11 members must have voted to recommend the intervention or assessment after 3 rounds of voting, and at most one member was allowed to vote other than “recommend” the intervention or assessment. On the basis of the discussion among the GWG members, adjustments to the wording of recommendations could be made between the voting rounds. If this level of consensus was not achieved, the GWG could have agreed to make a suggestion rather than a recommendation. No suggestion or statement could have been made if three or more members voted “no statement.” Differences of opinion within the GWG about ratings of strength of recommendation, if any, are described in the subsection “Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statement” for each statement.

Use of Guidelines to Enhance Quality of Care

Clinical practice guidelines can help enhance quality by synthesizing available research evidence and delineating recommendations for care on the basis of the available evidence. In some circumstances, practice guideline recommendations will be appropriate to use in developing quality measures. Guideline statements can also be used in other ways, such as educational activities or electronic clinical decision support, to enhance the quality of care that patients receive. Furthermore, when availability of services is a major barrier to implementing guideline recommendations, improved tracking of service availability and program development initiatives may need to be implemented by health organizations, health insurance plans, federal or state agencies, or other regulatory programs.
Typically, guideline recommendations that are chosen for development into quality measures will
advance one or more aims of the Institute of Medicine’s report on “Crossing the Quality Chasm”
(Institute of Medicine 2001) and the ongoing work guided by the multistakeholder-integrated AHRQ-led
National Quality Strategy by facilitating care that is safe, effective, patient-centered, timely, efficient,
and equitable. To achieve these aims, a broad range of quality measures (Watkins et al. 2015) is needed
that spans the entire continuum of care (e.g., prevention, screening, assessment, treatment, continuing
care), addresses the different levels of the health system hierarchy (e.g., system-wide, organization,
program/department, individual clinicians), and includes measures of different types (e.g., process,
outcome, patient-centered experience). Emphasis is also needed on factors that influence the
dissemination and adoption of evidence-based practices (Drake et al. 2008; Greenhalgh et al. 2004;

Measure development is complex and requires detailed development of specification and pilot testing
(Center for Health Policy/Center for Primary Care and Outcomes Research and Battelle Memorial
2011). Generally, however, measure development should be guided by the available evidence and
focused on measures that are broadly relevant and meaningful to patients, clinicians, and policy makers.
Measure feasibility is another crucial aspect of measure development but is often decided based on
current data availability, which limits opportunities for development of novel measurement concepts.
Furthermore, innovation in workflow and data collection systems can benefit from looking beyond
practical limitations in the early development stages in order to foster development of meaningful
measures.

Often, quality measures will focus on gaps in care or on care processes and outcomes that have
significant variability across specialties, health care settings, geographic areas, or patients’ demographic
characteristics. Administrative databases, registries, and data from electronic health records can help to
identify gaps in care and key domains that would benefit from performance improvements (Acevedo et
al. 2015; Patel et al. 2015; Watkins et al. 2016). Nevertheless, for some guideline statements, evidence
of practice gaps or variability will be based on anecdotal observations if the typical practices of
psychiatrists and other health professionals are unknown. Variability in the use of guideline-
recommended approaches may reflect appropriate differences that are tailored to the patient’s
preferences, treatment of co-occurring illnesses, or other clinical circumstances that may not have been
studied in the available research. On the other hand, variability may indicate a need to strengthen
clinician knowledge or address other barriers to adoption of best practices (Drake et al. 2008;
organizations, variability may reflect a need for quality improvement initiatives to improve overall
outcomes but could also reflect case-mix differences such as socioeconomic factors or the prevalence of
co-occurring illnesses.

When a guideline recommendation is considered for development into a quality measure, it must be
possible to define the applicable patient group (i.e., the denominator) and the clinical action or outcome
of interest that is measured (i.e., the numerator) in validated, clear, and quantifiable terms.
Furthermore, the health system’s or clinician’s performance on the measure must be readily ascertained

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from chart review, patient-reported outcome measures, registries, or administrative data. Documentation of quality measures can be challenging, and, depending on the practice setting, can pose practical barriers to meaningful interpretation of quality measures based on guideline recommendations. For example, when recommendations relate to patient assessment or treatment selection, clinical judgment may need to be used to determine whether the clinician has addressed the factors that merit emphasis for an individual patient. In other circumstances, standardized instruments can facilitate quality measurement reporting, but it is difficult to assess the appropriateness of clinical judgment in a validated, standardized manner. Furthermore, utilization of standardized assessments remains low (Fortney et al. 2017), and clinical findings are not routinely documented in a standardized format. Many clinicians appropriately use free text prose to describe symptoms, response to treatment, discussions with family, plans of treatment, and other aspects of care and clinical decision making. Reviewing these free text records for measurement purposes would be impractical, and it would be difficult to hold clinicians accountable to such measures without significant increases in electronic medical record use and advances in natural language processing technology. Conceptually, quality measures can be developed for purposes of accountability, for internal or health system–based quality improvement, or both. Accountability measures require clinicians to report their rate of performance of a specified process, intermediate outcome, or outcome in a specified group of patients. Because these data are used to determine financial incentives or penalties based on performance, accountability measures must be scientifically validated, have a strong evidence base, and fill gaps in care. In contrast, internal or health system–based quality improvement measures are typically designed by and for individual providers, health systems, or payers. They typically focus on measurements that can suggest ways for clinicians or administrators to improve efficiency and delivery of services within a particular setting. Internal or health system–based quality improvement programs may or may not link performance with payment, and, in general, these measures are not subject to strict testing and validation requirements. Quality improvement activities, including performance measures derived from these guidelines, should yield improvements in quality of care to justify any clinician burden (e.g., documentation burden) or related administrative costs (e.g., for manual extraction of data from charts, for modifications of electronic medical record systems to capture required data elements). Possible unintended consequences of any derived measures would also need to be addressed in testing of a fully specified measure in a variety of practice settings. For example, highly specified measures may lead to overuse of standardized language that does not accurately reflect what has occurred in practice. If multiple discrete fields are used to capture information on a paper or electronic record form, data will be easily retrievable and reportable, but oversimplification is a possible unintended consequence of measurement. Just as guideline developers must balance the benefits and harms of a particular guideline recommendation, developers of performance measures must weigh the potential benefits, burdens, and unintended consequences in optimizing quality measure design and testing. 

External Review
This guideline was made available for review in May-June 2019 by stakeholders, including the APA membership, scientific and clinical experts, allied organizations, and the public. In addition, a number of patient advocacy organizations were invited for input. <<NUMBER>> individuals and <<NUMBER>>
organizations submitted comments on the guideline (see the section “Individuals and Organizations That Submitted Comments” for a list of the names). The Chair and Co-chair of the GWG reviewed and addressed all comments received; substantive issues were reviewed by the GWG. **<<TO BE UPDATED>>**

**Funding and Approval**

This guideline development project was funded and supported by the APA without any involvement of industry or external funding. The guideline was submitted to the APA Assembly and APA Board of Trustees and approved on **<<MONTH DATE, YEAR>>** and **<<MONTH DATE, YEAR>>**, respectively.

**Glossary of Terms**

**Adequate dose** The dose of a medication at which therapeutic effects occurred when tested in clinical trials in a comparable population of subjects. This dose will differ for each medication and may need to be adjusted in an individual patient to address factors that would influence drug absorption, metabolism, elimination, or other pharmacokinetic properties.

**Adequate response** A reduction in symptoms as a result of treatment that is associated with clinically significant benefit in functioning and/or quality of life. A reduction in symptoms of 50% or more is sometimes used as a threshold for adequacy of response.

**Antipsychotic medication** One of a group of medications used in the treatment of psychosis. Some of the antipsychotic medications are also approved for use in other conditions such as mood disorders or Tourette’s syndrome. The first-generation antipsychotic (FGA) medications, sometimes referred to as “typical” antipsychotic medications, were the initial medications to be discovered. The FGAs include, but are not limited to, chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine. The second-generation antipsychotic (SGA) medications, sometimes referred to as “atypical” antipsychotic medications, include, but are not limited to, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Within each group of antipsychotic medications, there is significant variability in the pharmacological properties, presumed mechanisms, and side effect profiles of specific drugs.

**Assessment** The process of obtaining information about a patient through any of a variety of methods, including face-to-face interview, review of medical records, physical examination (by the psychiatrist, another physician, or a medically trained clinician), diagnostic testing, or history taking from collateral sources (American Psychiatric Association 2016).

**Capacity for decision making** The ability of an individual, when faced with a specific clinical or treatment-related decision, “to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices” (Appelbaum 2007, p. 1835).

**Comprehensive and person-centered treatment plan** A plan of treatment that is developed as an outgrowth of the psychiatric evaluation and is modified as clinically indicated. A comprehensive
treatment plan can include nonpharmacological treatments, pharmacological treatments, or both. It is
dividualized to the patient’s clinical presentation, safety-related needs, concomitant medical
conditions, personal background, relationships, life circumstances, and strengths and vulnerabilities.
There is no prescribed format that a comprehensive treatment plan must follow. The breadth and depth
of the initial treatment plan will depend on the amount of time and extent of information that are
available, as well as the needs of the patients and the care setting. Additions and modifications to the
treatment plan are made as additional information accrues (e.g., from family, staff, medical records, and
other collateral sources) and the patient’s responses to clinical interventions are observed.

Contraindication  A situation in which a drug or procedure should not be used because it may be
harmful to the patient.

Delusion  A false belief based on incorrect inference about external reality that is firmly held
despite what almost everyone else believes and despite what constitutes incontrovertible and obvious
proof or evidence to the contrary. The belief is not ordinarily accepted by other members of the
person’s culture or subculture (i.e., it is not an article of religious faith) (American Psychiatric Association
2013e). Their content may include a variety of themes (e.g., persecutory, referential, somatic, religious,
grandiose) (American Psychiatric Association 2013a).

Disorganized thinking  Disorganized thinking (also referred to as formal thought disorder) is typically
inferred from the individual’s speech and must be severe enough to substantially impair effective
communication. The individual may switch from one topic to another (derailment or loose associations),
provide answers to questions in an obliquely related or completely unrelated fashion (tangentiality) or
exhibit severely disorganized and nearly incomprehensible speech that resembles receptive aphasia in
its linguistic disorganization (incoherence or “word salad”).

Grossly disorganized or abnormal motor behavior  Grossly disorganized or abnormal motor
behavior may manifest itself in a variety of ways, ranging from childlike “silliness” to unpredictable
agitation. Problems may be noted in any form of goal-directed behavior, leading to difficulties in
performing activities of daily living. Catatonic behavior is another manifestation of abnormal motor
behavior and can range from resistance to instructions (negativism); to maintaining a rigid,
inappropriate or bizarre posture; to a complete lack of verbal and motor responses (mutism and stupor).
It can also include purposeless and excessive motor activity without obvious cause (catatonic
excitement). Other features are repeated stereotyped movements, staring, grimacing, mutism, and the
echoing of speech.

Hallucination  Hallucinations are perception-like experiences that occur without an external stimulus.
They are vivid and clear, with the full force and impact of normal perceptions, and not under voluntary
control. They may occur in any sensory modality (American Psychiatric Association 2013a).

Hepatic failure  Deterioration of liver function that results in coagulation abnormality (usually an
international normalized ratio greater than or equal to 1.5) and any degree of mental alteration
(encephalopathy). Although there is no identifiable cause in approximately 15% of cases of acute
hepatic failure, typical etiologies include drug-induced liver injury, viral hepatitis, autoimmune liver disease, and shock or hypoperfusion (Lee et al. 2011).

**Hepatic impairment** Inability of the liver to function normally; typically defined in severity according to laboratory values and clinical characteristics as reflected by the Child-Pugh score or the Model for End-Stage Liver Disease (MELD) score (Ghany and Hoofnagle et al. 2018; Food and Drug Administration 2003).

**Hopelessness** Feeling of despair about the future out of the belief that there is no possibility of a solution to current problems or a positive outcome.

$I^2$ A statistical estimate of the proportion of the variance that is due to heterogeneity.

**Impulsivity** Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing and following plans; having a sense of urgency and exhibiting self-harming behavior under emotional distress (American Psychiatric Association 2013f).

**Initial psychiatric evaluation** A comprehensive assessment of a patient that has the following aims: identify the reason that the patient is presenting for evaluation; establish rapport with the patient; understand the patient’s background, relationships, current life circumstances, and strengths and vulnerabilities; establish whether the patient has a psychiatric condition; collect information needed to develop a differential diagnosis and clinical formulation; identify immediate concerns for patient safety; and develop an initial treatment plan or revise an existing plan in collaboration with the patient.

Relevant information may be obtained by interviewing the patient; reviewing prior records; or obtaining collateral information from treating clinicians, family members, or others involved in the patient’s life. Physical examination, laboratory studies, imaging, psychological or neuropsychological testing, or other assessments may also be included. The psychiatric evaluation may occur in a variety of settings, including inpatient or outpatient psychiatric settings and other medical settings. The evaluation is usually time intensive. The amount of time spent depends on the complexity of the problem, the clinical setting, and the patient’s ability and willingness to cooperate with the assessment. Several meetings with the patient (and family or others) over time may be necessary. Psychiatrists may conduct other types of evaluations that have other goals (e.g., forensic evaluations) or that may be more focused and circumscribed than a psychiatric evaluation as defined here. Guidelines are not intended to address such evaluations (American Psychiatric Association 2016).

**Negative symptoms** Negative symptoms can be prominent in schizophrenia and include diminution of emotional expression (reductions in the expression of emotions in the face, eye contact, intonation of speech, and movements of the hand, head, and face), decrease in motivated self-initiated purposeful activities (avolition), diminution of speech output (alogia), decrease in the ability to experience pleasure from positive stimuli (anhedonia), or apparent lack of interest in social interactions (asociality).

**Over-the-counter medications or supplements** Drugs or supplements that can be bought without a prescription.
Renal impairment  Inability of the kidney(s) to function normally, typically described in terms of reductions in creatinine clearance or estimated glomerular filtration rate (eGFR). An eGFR of 60–89 mL/min/1.73 m² indicates mildly reduced kidney function, an eGFR of 30–59 mL/min/1.73 m² indicates moderately reduced kidney function, an eGFR of 15–29 mL/min/1.73 m² indicates severely reduced kidney function, and an eGFR of less than 15 mL/min/1.73 m² indicates a very severe reduction in kidney function or end-stage renal disease (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013).

Suicidal ideas  Thoughts of serving as the agent of one’s own death.

Suicide Death caused by self-directed injurious behavior with any intent to die as a result of the behavior (Crosby et al. 2011).

Suicide attempt  A nonfatal, self-directed, potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not result in injury (Crosby et al. 2011). It may be aborted by the individual or interrupted by another individual.

Suicide intent  Subjective expectation and desire for a self-injurious act to end in death.

Suicide means  The instrument or object used to engage in self-inflicted injurious behavior with any intent to die as a result of the behavior.

Suicide method  The mechanism used to engage in self-inflicted injurious behavior with any intent to die as a result of the behavior.

Suicide plan  Delineation of the method, means, time, place, or other details for engaging in self-inflicted injurious behavior with any intent to die as a result of the behavior.

Therapeutic alliance  A characteristic of the relationship between the patient and clinician that describes the sense of collaboration in pursuing therapeutic goals as well as the patient’s sense of attachment to the clinician and perception of whether the clinician is helpful (Gabbard 2009).

Trauma history  A history of events in the patient’s life with the potential to have been emotionally traumatic, including but not limited to exposure to actual or threatened death, serious injury, illness, or sexual violence. Exposure may occur through direct experience or by observing an event in person or through technology (e.g., television, audio/video recording) or by learning of an event that occurred to a close family member or close friend. Trauma could also include early adversity, neglect, maltreatment, emotional abuse, physical abuse, or sexual abuse occurring in childhood; exposure to natural or man-made disasters; exposure to combat situations; being a victim of a violent crime; involvement in a serious motor vehicle accident; or having serious or painful or prolonged medical experiences (e.g., intensive care unit stay).

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Disclosures

The Guideline Writing Group and Systematic Review Group reported the following disclosures during development and approval of this guideline:

Dr. Keepers is employed as Professor and Chair of the Department of Psychiatry by Oregon Health & Sciences University. He receives travel funds from the American Board of Psychiatry and Neurology, the American College of Psychiatry, and the Accreditation Council for Graduate Medical Education related to his activities as a member or chair of various committees. He reports no conflicts of interest with his work on this guideline.

Dr. Fochtmann is employed by Stony Brook University where she is a Distinguished Service Professor of psychiatry, pharmacological sciences, and biomedical informatics. She also serves as a Deputy Chief Medical Information Officer for Stony Brook Medicine. Dr. Fochtmann has received payment for grant reviews for the National Institute of Mental Health (NIMH) and is a co-investigator on a grant funded by NIMH. She consults for the American Psychiatric Association on the development of practice guidelines and has received travel funds to attend meetings related to these duties. She reports no conflicts of interest with her work on this guideline.

Dr. Anzia is employed as a professor of psychiatry and behavioral sciences and residency program director/vice chair for education at Northwestern University/Feinberg School of Medicine. She receives part of her salary from the Medical Staff Office of Northwestern Medicine for her role as Physician Health Liaison. Dr. Anzia receives travel funds from the American Board of Psychiatry and Neurology, the American College of Psychiatry, and the Accreditation Council for Graduate Medical Education for her activities as Board Director, committee chair, and various other committees. She has no conflicts of interest with work on the guidelines.

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publisher of educational materials designed to improve neuropsychiatric assessment skills. Any income received is used to off-set production and development costs of the materials. He reports no conflicts of interest with his work on this guideline.

Dr. Lyness is employed as Senior Associate Dean for Academic Affairs and Professor of Psychiatry & Neurology in the School of Medicine & Dentistry at the University of Rochester Medical Center. He receives compensation for his work as a psychiatry director of the American Board of Psychiatry & Neurology, Inc. At times he provides independent medical examinations for various attorneys. He has no other relevant financial or fiduciary interests and reports no conflicts of interest with his work on this guideline.

Dr. Mojtabai is employed as a professor of public health at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, and as a psychiatrist at Johns Hopkins Hospital. During the period of preparation of this guideline, he received royalties from UpToDate, Inc. and consulting fees from the RAND Corporation. He reports no conflicts of interest with his work on this guideline.

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Dr. Degenhardt is employed as a fifth-year resident in psychiatry at the University of British Columbia in Canada by Vancouver Coastal Health. She is a member of the APA Council of Research and APA Leadership fellowship. She is also on the board of directors of the Canadian Psychiatric Association (CPA), Chair of the CPA Members-in-Training Executive Committee, and various other committees. She has received travel funds to attend meetings related to these duties. She reports no conflicts of interest with her work on this guideline.

Individuals and Organizations That Submitted Comments

<<TO BE UPDATED>>
Appendices: Review of Research Evidence

Appendix A. Clinical Questions

Clinical Questions

The following key questions formed the basis of the AHRQ review:

1a. What are the comparative benefits and harms of pharmacological treatments for adults with schizophrenia?

1b. How do the benefits and harms of pharmacological treatments for adults with schizophrenia vary by patient characteristics?

2a. What are the benefits and harms of psychosocial and other nonpharmacological treatments for adults with schizophrenia?

2b. How do the benefits and harms of psychosocial and other nonpharmacological treatments for adults with schizophrenia vary by patient characteristics (e.g., age, sex, race, ethnicity, socioeconomic status, time since illness onset, prior treatment history, co-occurring psychiatric disorders, pregnancy)?

The following key questions formed the basis of searches related to neurological side effects of antipsychotic medications:

1. What are the comparative benefits and harms of pharmacological treatments for acute dystonia associated with antipsychotic therapy?

2. What are the comparative benefits and harms of pharmacological treatments for parkinsonism associated with antipsychotic therapy?

3. What are the comparative benefits and harms of pharmacological treatments for akathisia associated with antipsychotic therapy?

4. What are the comparative benefits and harms of pharmacological treatments for tardive syndromes associated with antipsychotic therapy?

Appendix B. Search Strategies, Study Selection, and Search Results

AHRQ review

The AHRQ’s systematic review, Treatments for Schizophrenia in Adults (McDonagh et al. 2017), served as the predominant source of information for this guideline. Databases that were searched are Ovid MEDLINE® (PubMed®), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO®. Results were limited to English-language, adult (18 and older), and human-only studies. The search varied by Key Question as high-quality systematic reviews were used as a starting point for the review. For Key Question 1, search dates for first-generation antipsychotic medications (FGAs) versus second-generation antipsychotic medications (SGAs) began in 2011 and for SGAs versus SGAs began in 2013. Key Question 2 did not restrict the start date. All searches were
conducted through February 1, 2017. The search strategies used can be found in Appendix A of the AHRQ review (McDonagh et al. 2017).

The AHRQ review (McDonagh et al. 2017) adhered to the procedures outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Agency for Healthcare Research and Quality 2014). Recent, comprehensive, good- or fair-quality systematic reviews served as a primary source of evidence supplemented by information from randomized controlled trials (RCTs) published since the systematic reviews or when no systematic reviews were available. For assessment of harms of treatment, systematic reviews of observational trials were also included. Eligibility for inclusion and exclusion of articles adhered to pre-established criteria. Specifically, the AHRQ review included articles that had at least 12 weeks of follow-up and were conducted in outpatient settings in countries that were relevant to the United States’ health care system. Articles that addressed benefits of treatment were included if at least 90% of the sample had a diagnosis of schizophrenia (or schizophreniform disorder) with a schizophrenia spectrum disorder in at least 50% of the sample (minimum sample size > 50) for studies of harms of treatment. For key questions that related to antipsychotic treatment, all of the SGAs were included and of FGAs, studies on fluphenazine, haloperidol, and perphenazine were included. Only head-to-head comparison studies were included. For studies of psychosocial and other nonpharmacological interventions, studies were included if they compared usual care, standard care, treatment as usual, or a waitlist control group to active treatment with assertive community treatment, cognitive adaptive training, cognitive behavioral therapy, cognitive remediation, early interventions for first episode psychosis, family interventions, intensive case management, illness self-management training, interventions for co-occurring schizophrenia and substance use, psychoeducation, social skills training, supported employment, or supportive psychotherapy.

Using these criteria, titles and abstracts were reviewed by two individuals (McDonagh et al. 2017). Full text articles were retrieved if either reviewer felt inclusion was warranted. Full text articles were also evaluated by two reviewers and disagreements about inclusion were resolved by consensus. Included studies are listed in Appendix B of the AHRQ review and excluded studies (with the reason for exclusion) are listed in Appendix C of the AHRQ review (McDonagh et al. 2017). For Key Question 1 on antipsychotic treatment, there were 698 citations identified of which 519 were excluded based on title and abstract review, yielding 179 full text articles that were reviewed, of which 38 were included in the final AHRQ review. For Key Question 2 on psychosocial and other nonpharmacological interventions, there were 2766 citations identified of which 1871 were excluded based on title and abstract review, yielding 895 full text articles that were reviewed, of which 53 were included in the final AHRQ review. Additional summary information about the included studies is shown in Table B-1 and additional details can be found in the AHRQ review (McDonagh et al. 2017).

For included studies, abstracted information was verified for accuracy and completeness by a second individual and included citation, year, study design, setting, funding source, country, sample size, eligibility criteria, clinical characteristics, and other characteristics of the study design, population, intervention, and outcomes (McDonagh et al. 2017). In addition, individual controlled trials and systematic reviews were assessed by two team members with predefined criteria for study quality, yielding ratings of “good,” “fair,” or “poor” with disagreements resolved by consensus (McDonagh et al. 2017).
Included systematic reviews were generally of good quality whereas additional included studies were generally of fair quality.

Table B-1. Studies used in AHRQ Review (adapted from McDonagh et al. 2017)

<table>
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<th>Treatment of neurological side effects of antipsychotic medications</th>
<th>Systematic reviews</th>
<th>Number of publications</th>
<th>Number of trials in systematic reviews</th>
<th>Number of subjects in systematic reviews</th>
<th>Number of additional trials</th>
<th>Number of publications</th>
<th>Number of subjects in additional trials</th>
<th>Total Number of subjects</th>
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<td>0</td>
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<td>Social skills training</td>
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<td>4</td>
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<td>433</td>
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<tr>
<td>Supported employment</td>
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<td>2</td>
<td>3</td>
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<td>3,742</td>
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<tr>
<td>Supportive psychotherapy</td>
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<td>1</td>
<td>5</td>
<td>822</td>
<td>0</td>
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</tr>
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</table>
parkinsonism, akathisia, tardive syndromes, or neuroleptic malignant syndrome. Systematic reviews and
meta-analyses were used as a primary source of evidence and if multiple Cochrane reviews on a topic
had been done, only the most recent review was included. For topics on which no systematic review was
available, RCTs were included with a sample size of at least 20 subjects and observational studies were
included with a sample of at least 50 individuals. Included studies had a follow-up period of at least 1
week for acute dystonia or neuroleptic malignant syndrome and 8 weeks for other side effects.

Table B-2. Strategy for MEDLINE (PubMed) search on treatments for neurological side effects of
antipsychotic medications

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<thead>
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<th>Search Term</th>
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<td>#8</td>
<td>Search #7 NOT #4</td>
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<td>#9</td>
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Table B-3. Strategy for Cochrane Library search on treatments for neurological side effects of antipsychotic medications
#2  "9-hydroxy-risperidone" or "abilify" or "antipsychotic" or "antipsychotics" or "aripiprazole" or "Asenapine" or "Chlorpromazine" or "Chlorprothixene" or "Clopixol" or "clozapine" or "clozaril" or "Consta" or "droperidol" or "Fanapt" or "Fazaclor" or "Fluanxol" or "flupenthixol" or "flupenthixol" or "fluphenazine depot" or "fluphenazine enanthate" or "Fluphenazine" or "Geodon" or "Haldol" or "haloperidol decanoate" or "haloperidol" or "Illoperidone" or "Inapsine" or "Invega" or "Largactil" or "Loxapac" or "Loxapine" or "Loxitane" or "Lurasidone" or "Mellaril" or "Mesoridazine" or "Moban" or "Modecate" or "Molindone" or "Navane" or "olanzapine" or "Orap" or "Paliperidone" or "Perphenazine" or "Pimozide" or "Prolixin" or "quetiapine" or "Relprevv" or "Risperdal" or "Risperidone" or "Saphris" or "Serentil" or "Seroquel" or "Stelazine" or "Sustenna" or "Symbyax" or "Taractan" or "Thioridazine" or "Thiothixene" or "Thorazine" or "Trifluoperazine" or "Trilafon" or "Zelcord" or "ziprasidone" or "zuclopenthixol" or "Zydis" or "Zyprexa"

#3  "akathisia" or "drug induced parkinsonism" or "dystonic reaction" or "dystonic reactions" or "extrapyramidal reactions" or "extrapyramidal side effect" or "extrapyramidal side effects" or "extrapyramidal signs" or "extrapyramidal syndrome" or "extrapyramidal syndromes" or "neuroleptic malignant" or "tardive dyskinesia" or "tardive dystonia" or "neuroleptic induced parkinsonism" or "medication induced parkinsonism" or "tardive akathisia"

#4  (#1 and #2) or (#1 and #3) or (#2 and #3)  

Limited to Cochrane Reviews, Other Reviews and Trials

Full text documents were then reviewed by one individual (L.J.F.) to determine whether they met eligibility criteria.

For tardive dyskinesia, 12 systematic reviews were available with two reviews of multiple treatment approaches and one review each related to anticholinergic medication, cholinergic medication, benzodiazepines, Vitamin B6, Vitamin E, calcium channel blockers, gamma-aminobutyric acid agonists, non-antipsychotic catecholaminergic drugs, miscellaneous treatments, and antipsychotic reduction or cessation. For akathisia, three recent systematic reviews were available with one review each related to beta-adrenergic blocking agents, anticholinergic agents, and mirtazapine. No additional RCTs or observational studies met inclusion criteria for other treatments of akathisia (e.g., benzodiazepines). For neuroleptic-induced parkinsonism, one systematic review was available, but evidence was insufficient to draw any definitive conclusions. For acute dystonia, one systematic review, one RCT and one non-randomized prospective study examined effects of anticholinergic medications in reducing the likelihood of acute dystonia, however, no studies meeting inclusion criteria examined use of anticholinergic agents as a treatment of acute dystonia. In addition, no studies meeting inclusion criteria were found that addressed treatment of neuroleptic malignant syndrome.
Appendix C. Review of Research Evidence Supporting Guideline Statements

Assessment and Treatment Plan

Statement 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, a review of psychiatric symptoms and trauma history, a substance use assessment, a psychiatric treatment history, an assessment of physical health, an assessment of psychosocial and cultural factors, 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).

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. Expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves diagnostic accuracy, appropriateness of treatment selection, and treatment safety. For additional details, see Guideline I, “Review of Psychiatric Symptoms, Trauma History, and Psychiatric Treatment History,” Guideline II. "Substance Use Assessment," Guideline III. "Assessment of Suicide Risk," Guideline IV. "Assessment of Risk for Aggressive Behaviors," Guideline V. "Assessment of Cultural Factors," and Guideline VI, “Assessment of Medical Health,” in the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association 2016). A detailed systematic review to support this statement was outside the scope of this guideline; however, less comprehensive searches of the literature did not yield any studies related to this recommendation in the context of schizophrenia treatment. Consequently, the strength of research evidence is rated as low.

Statement 2

APA recommends (1C) that the initial psychiatric evaluation of a patient with a possible psychotic disorder include a quantitative measure to identify symptoms that may be the focus of treatment and to determine their severity.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. Consequently, the strength of research evidence is rated as low. Expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves diagnostic accuracy, appropriateness of treatment selection, and longitudinal assessment of patient symptoms and treatment effects. This recommendation is also consistent with Guideline VII on Quantitative Assessment as part of the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association 2016).

Statement 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.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. A detailed systematic review to support this statement was outside the scope of this guideline; however, less comprehensive searches of the literature did not yield any studies that directly related to
this recommendation in the context of schizophrenia treatment. Consequently, the strength of research
evidence is rated as low. Nevertheless, in the bulk of the literature reviewed in the AHRQ report
(McDonagh et al. 2017), pharmacotherapy was included in all treatment arms in the studies of
psychosocial interventions. Invariably, in studies of pharmacotherapies, some additional form of clinical
intervention is incorporated into treatment and can include elements of patient education, supportive
psychotherapy, or other brief interventions.

Pharmacotherapy

Statement 4

APA recommends (1A) that patients with schizophrenia be treated with an antipsychotic medication
and monitored for effectiveness and side effects.*

Evidence for this statement comes from the AHRQ review (McDonagh et al. 2017) as well as from other
high-quality meta-analyses that examined findings from placebo-controlled trials of antipsychotic
medications in schizophrenia. The data from placebo-controlled trials is essential in making an initial
determination of whether the benefits of antipsychotic medications outweigh the harms of
antipsychotic medications. Placebo-controlled trial data as well as findings from head-to-head
comparison studies and network analyses provide additional information on whether the benefits and
harms of specific antipsychotic medications suggest preferential use (or non-use) as compared to other
antipsychotic medications. The strength of the guideline statement is rated as high in demonstrating
that the benefits of treatment with an antipsychotic medication outweigh the harms, although harms
are clearly present and must be taken into consideration.

Primary evidence for placebo-controlled antipsychotic trial data came from the systematic review,
Bayesian meta-analysis, and meta-regression conducted by Leucht and colleagues (Leucht et al. 2017),
which included 167 studies (total N=28,102) published from 1955 to 2016 that were randomized and
double-blinded with placebo control groups. The authors excluded studies of acute treatment with
short-acting intramuscular antipsychotic medications and relapse prevention (including studies of LAI
antipsychotic agents). Studies of clozapine were excluded due to possible superior efficacy and studies
conducted in China were excluded due to concerns about study quality. Studies were also excluded if
subjects had primarily negative symptoms or significant comorbidity, either in psychiatric or physical
health conditions. The median study duration was 6 weeks with almost all studies lasting 12 weeks or
less in terms of primary study outcomes. None of the studies were focused on first-episode or
treatment-resistant samples of subjects and the mean illness duration was 13.4 (standard deviation (SD)
4.7) years with a mean subject age of 38.7 (SD 5.5). The number of studies available on each drug was
highly variable with chlorpromazine, haloperidol, olanzapine, and risperidone being most often studied
and limited information available on some antipsychotic medications.

* 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.
Table C-1. Results of meta-analysis on placebo-controlled trials of antipsychotic treatment (data extracted from Leucht et al. 2017)

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>Number of subjects</th>
<th>Measure</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All studies</td>
<td>105</td>
<td>22,741</td>
<td>Mean effect size=0.47</td>
<td>0.42, 0.51</td>
<td>52%</td>
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<tr>
<td>Any response with drug</td>
<td>97</td>
<td>20,690</td>
<td>Response ratio=1.93</td>
<td>1.72, 2.19</td>
<td></td>
<td>NNT=6</td>
</tr>
<tr>
<td>vs. placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Good response</td>
<td>30</td>
<td>8,408</td>
<td>Response ratio=1.96</td>
<td>1.65, 2.44</td>
<td></td>
<td>NNT=8; 23% good response with antipsychotic vs. 14% with placebo</td>
</tr>
<tr>
<td>At least minimal response</td>
<td>46</td>
<td>8,918</td>
<td>Response ratio=1.75</td>
<td>1.59, 1.07</td>
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<td>NNT=5; 51% minimal response with antipsychotic vs. 30% with placebo</td>
</tr>
<tr>
<td>Discontinuation for any</td>
<td>105</td>
<td>22,851</td>
<td>Risk ratio=1.25</td>
<td>1.20, 1.31</td>
<td></td>
<td>NNT=11; 38% discontinuation with antipsychotic vs. 56% with placebo</td>
</tr>
<tr>
<td>reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation for</td>
<td>94</td>
<td>23,017</td>
<td>Risk ratio=2.09</td>
<td>1.90, 2.32</td>
<td></td>
<td>NNT=7; 13% discontinuation with antipsychotic vs. 26% with placebo</td>
</tr>
<tr>
<td>inefficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Positive symptoms</td>
<td>64</td>
<td>18,174</td>
<td>SMD=0.45</td>
<td>0.40, 0.50</td>
<td>56%</td>
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<td>Negative symptoms</td>
<td>69</td>
<td>18,632</td>
<td>SMD=0.35</td>
<td>0.31, 0.40</td>
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<tr>
<td>Depression</td>
<td>33</td>
<td>9,658</td>
<td>SMD=0.27</td>
<td>0.20, 0.34</td>
<td>50%</td>
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<tr>
<td>Quality of life</td>
<td>6</td>
<td>1,900</td>
<td>SMD=0.35</td>
<td>0.16, 0.51</td>
<td>43%</td>
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<td>Social functioning</td>
<td>10</td>
<td>3,077</td>
<td>SMD=0.34</td>
<td>0.21, 0.47</td>
<td>46%</td>
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<tr>
<td>Use of antiparkinsonian</td>
<td>63</td>
<td>14,942</td>
<td>Risk ratio=1.93</td>
<td>1.65, 2.29</td>
<td></td>
<td>NNH=12; 19% with antipsychotic vs. 10% with placebo</td>
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<td>medications</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sedation</td>
<td>86</td>
<td>18,574</td>
<td>Risk ratio=2.80</td>
<td>2.30, 3.55</td>
<td>54</td>
<td>14% with antipsychotic vs. 6% with placebo</td>
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<tr>
<td>Weight gain</td>
<td>59</td>
<td>15,219</td>
<td>SMD=-0.43</td>
<td>-0.55, -0.30</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Prolactin increase</td>
<td>51</td>
<td>15,219</td>
<td>SMD=-0.43</td>
<td>-0.55, -0.30</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>29</td>
<td>9,833</td>
<td>SMD=-0.19</td>
<td>-0.29, -0.08</td>
<td>80</td>
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</table>

SMD=standardized mean difference, NNT=number needed to treat, NNH=number needed to harm
The authors found a moderate benefit of antipsychotic medications, with positive symptoms improving the most but improvements in negative symptoms, depression, quality of life, and social functioning also noted with treatment (Leucht et al. 2017). Side effects were also present but differed substantially among medications. They also found, however, that effect sizes for antipsychotic medications have decreased with time over the past 60 years. This seems to result from increasing placebo response rates rather than decreasing medication response, although the benefit of haloperidol as compared to placebo has decreased with time. Not surprisingly, these trends are likely to confound comparisons of newer versus older medications. Although industry sponsorship was associated with a lower effect size as compared to studies funded by other mechanisms, publication bias was observed because of the tendency to avoid publishing studies with no effect of treatment.

In the AHRQ review (McDonagh et al. 2017), there were few head-to-head comparison studies available for most of the antipsychotic medications. In terms of functioning, the strength of evidence (SOE) was low. Older SGAs (risperidone, olanzapine, quetiapine, ziprasidone) and paliperidone did not differ in terms of global functioning or employment rates, although social functioning with risperidone in a long-acting injectable (LAI) formulation was better than with quetiapine in a single study (Rouillon et al. 2013). Measures of quality of life also showed no difference among older SGAs or between older SGAs and FGAs (specifically, haloperidol and perphenazine), based on a low to moderate SOE.

In terms of response rates (McDonagh et al. 2017), there was no difference between haloperidol and risperidone (16 RCTs, N=3,452; relative risk (RR) 0.94, 95% confidence interval (CI) 0.87 to 1.02; moderate SOE), aripiprazole (five RCTs, N=2,185; RR 1.01, 95% CI 0.76 to 1.34; low SOE), quetiapine (six RCTs, N=1,421; RR 0.99, 95% CI 0.76 to 1.30; low SOE), and ziprasidone (6 RCTs, N=1,283; RR 0.98, 95% CI 0.74 to 1.30; low SOE). However, response with olanzapine was significantly better than with haloperidol (14 RCTs, N=4,099; RR 0.86, 95% CI 0.78 to 0.96; low SOE). In addition, a network meta-analysis of 46 head-to-head RCTs showed a significantly greater likelihood of response with olanzapine (odds ratio (OR) 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) than quetiapine (low SOE). Olanzapine was also associated with higher remission rates as compared to haloperidol (three RCTs, pooled RR 0.65, 95% CI 0.45 to 0.94; I²=54%; low SOE) but there was no difference in remission rates between haloperidol and ziprasidone based on three trials (three RCTs, RR 0.89, 95% CI 0.71 to 1.12; low SOE).

In terms of core illness symptoms (e.g., delusions, hallucinations, disorganized thinking), all SGAs that were studied were superior to placebo (standardized mean difference (SMD) -0.33 to -0.88; low SOE; McDonagh et al. 2017). Risperidone (21 RCTs, N=4,020; mean difference 3.24, 95% CI 1.62 to 4.86) and olanzapine (15 RCTs, N=4,209; mean difference (MD) 2.31, 95% 0.44 to 4.18) were associated with greater improvements in total Positive and Negative Syndrome Scale (PANSS) score as compared to haloperidol (moderated SOE) but no differences were noted in other comparisons of FGAs and SGAs (low SOE). With comparisons among SGAs, clozapine improved core illness symptoms more than other SGAs except for olanzapine (network meta-analysis of 212 RCTs; SMDs on PANSS or Brief Psychiatric Rating Scale (BPRS) -0.32 to -0.55; low SOE); olanzapine and risperidone improved core illness symptoms.
more than the other SGAs except for each other and paliperidone (SMDs -0.13 to -0.26; low SOE); and paliperidone improved core illness symptoms more than lurasidone and iloperidone (SMDs -0.17; low SOE).

For negative symptoms (McDonagh et al. 2017), haloperidol was less effective than olanzapine (five RCTs, N=535; MD based on the Scale for the Assessment of Negative Symptom scores 2.56, 95% CI 0.94 to 4.18; moderate SOE), aripiprazole (three RCTs, N=1,701; MD 0.80, 95% CI 0.14 to 1.46), olanzapine (14 RCTs, N=3,742; MD 1.06, 95% CI 0.46 to 1.67), and risperidone (22 RCTs, N=4,142; MD 0.80, 95% CI 0.14 to 1.46), with the latter findings based on negative symptom scores of the PANSS and having a low SOE. Other comparisons of FGAs versus SGAs showed no effects on negative symptoms (low SOE).

Few studies assessed effects of antipsychotic medications on self-harm but, among patients at high risk, the InterSePT trial (Meltzer et al. 2003) found that clozapine was superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide (hazard ratio (HR) 0.76, 95% CI 0.58 to 0.97; low SOE).

Overall discontinuation rates and time to discontinuation reflect whether a treatment is effective but also whether it is tolerable. In this regard, a network meta-analysis of 111 studies (McDonagh et al. 2017) found that rates of discontinuation were less with:

- Olanzapine and clozapine as compared to asenapine, cariprazine, iloperidone, lurasidone, olanzapine LAI, quetiapine, risperidone, and ziprasidone (ORs range from 0.42 for clozapine versus iloperidone to 0.69 for clozapine versus risperidone)
- Clozapine as compared to LAI paliperidone palmitate monthly (OR 0.56, 95% CI 0.33 to 0.96)
- Olanzapine as compared to paliperidone (OR 0.67, 95% CI 0.50 to 0.89)
- Quetiapine ER as compared to iloperidone, olanzapine LAI, or quetiapine (ORs 0.26 to 0.35)
- Risperidone and aripiprazole as compared to iloperidone or quetiapine (ORs 0.61 to 0.77).
- Risperidone and LAI aripiprazole monthly as compared to iloperidone (ORs 0.52 and 0.62, respectively).

Findings on time to discontinuation are more limited and need replication (low SOE), but suggest that olanzapine may have a longer time to discontinuation than quetiapine, risperidone, and ziprasidone (4 months based on trial data; 1.5-2.2 months shorter based on observational data); clozapine may have a longer time to discontinuation than olanzapine, risperidone, or quetiapine (7.2 to 7.8 months in Phase 2E of the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study); and LAI risperidone may have a longer time to discontinuation than aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone (2.6 to 4 months).

A network meta-analysis (McDonagh et al. 2017), which used data from 90 head-to-head trials of greater than 6-weeks duration, found the risk of withdrawals due to adverse events was less with:

- LAI risperidone as compared to clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine extended release (ER) (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82).
• olanzapine as compared to clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.19 to 0.79); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82).

• aripiprazole as compared to clozapine (OR 0.43, 95% CI 0.21 to 0.88) and ziprasidone (OR 0.64, 95% CI 0.44 to 0.94).

• cariprazine as compared to clozapine (OR 0.40, 95% CI 0.17 to 0.95).

• iloperidone as compared to clozapine (OR 0.34, 95% CI 0.13 to 0.91).

These findings had a low SOE. For haloperidol, withdrawals due to adverse events were significantly higher than with SGAs (moderate SOE), specifically, aripiprazole (eight RCTs, N=3,232; RR 1.25, 1.07 to 1.47; I²=0%), olanzapine (24 RCTs, N=5,708; RR 1.89, 95% CI 1.57 to 2.27; I²=0%), risperidone (25 RCTs, N=4,581; RR 1.32, 95% CI 1.09 to 1.60; I²=0%), and ziprasidone (seven RCTs, N=1,597; RR 1.68, 95% CI 1.26 to 2.23; I²=0%).

Overall adverse event rates also favored SGAs as compared to haloperidol (moderate SOE), specifically aripiprazole (three RCTs, N=1,713; RR 1.11, 95% CI 1.06 to 1.17; I²=0%), risperidone (eight RCTs, N=1313; RR 1.20, 95% CI 1.01 to 1.42; I²=84%), and ziprasidone (six RCTs, N=1,448; RR 1.13, 95% CI 1.03 to 1.23; I²=31%). Among comparisons between SGAs, no differences in overall adverse events were noted (low to moderate SOE).

In terms of mortality, comparisons were difficult because of the short duration of most studies and the small number of reported events in these clinical trials (incidence rates 0 to 1.17%). Nevertheless, there were no significant mortality differences found between asenapine and olanzapine (two RCTs; RR 2.49, 95% CI 0.54 to 11.5; low SOE), quetiapine and risperidone (two RCTs; RR 3.24, 95% CI 0.72 to 14.6; low SOE), and LAI paliperidone palmitate (monthly) versus risperidone LAI (two RCTs; RR 1.26, 95% CI 0.21 to 7.49; low SOE). Additional findings from retrospective cohort studies found no significant difference in the risk of all-cause (one study, N=48,595) or cardiovascular mortality (two studies, N=55,582) between risperidone, olanzapine, and quetiapine (low SOE).

For the additional harms data described in the AHRQ report (McDonagh et al. 2017), evidence was relatively limited and did not adjust for known factors that confound risk. Data on cardiac disease is mixed. A large, good-quality retrospective cohort study found no significant differences in the risk of cardiovascular death, acute coronary syndrome, or ischemic stroke between risperidone and olanzapine or quetiapine in patients age 18 to 64 years within the first year of starting the drug. However, a large adverse event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy, whereas olanzapine, quetiapine, and risperidone were not. In contrast, other limited evidence suggested an increased risk of cardiac arrest and arrhythmia with risperidone compared with clozapine and data from CATIE suggest a higher estimated 10-year risk of coronary heart disease with olanzapine compared with risperidone. As compared to FGAs, the SGA aripiprazole showed a lower likelihood of cardiomyopathy or coronary heart disease.

Findings on neurological side effects such as akathisia and parkinsonism also showed significant variability among the head-to-head comparison studies, which makes it difficult to draw overall...
conclusions about side effect rates or risk. For new-onset tardive dyskinesia, overall rates were low (3% of subjects treated with risperidone as compared to 1% to 2% for other medications). Nevertheless, findings from observational trials suggested a significant increase in risk with risperidone as compared with olanzapine (OR 1.70, 95% CI 1.35 to 2.14).

Metabolic effects varied with study duration, but clinically important weight gain (defined as a 7% or more increase from baseline) was greater with olanzapine than with ariprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81), and ziprasidone (RR 5.76) across 3.7 to 24 months. Olanzapine had a significantly greater risk of metabolic syndrome than risperidone (pooled OR 1.60, 95% CI 1.10 to 2.21; I²=0%; follow-up of 6 weeks to 3 months) or ariprazole (pooled OR 2.50, 95% CI 1.32 to 4.76; I²=0%; follow-up of 3.5 to 12 months). In adults, observational evidence indicated an increased risk of new-onset diabetes with olanzapine compared with risperidone (OR 1.16, 95% CI 1.03 to 1.31). A single study found diabetic ketoacidosis to be increased with olanzapine compared with risperidone (OR 3.5, 95% CI 1.7 to 7.9) whereas a second study found no difference in diabetic ketoacidosis, hyperglycemia, or hyperglycemic hyperosmolar state between risperidone and olanzapine, regardless of age group, but a significantly lower risk with quetiapine compared with risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90).

Taken together, the findings of the AHRQ review (McDonagh et al. 2017) complement the meta-analysis of Leucht and colleagues (Leucht et al. 2017) in showing efficacy of antipsychotic medications, particularly for core illness symptoms but also for other outcomes. Furthermore, research evidence demonstrates no clear and consistent superiority of one antipsychotic medication as compared to other antipsychotic medications. In addition, the systematic reviews suggest considerable variability in side effect profiles among antipsychotic medications without a clear continuum of risk for individual medications when all side effects are considered.
**Statement 5**

APA recommends (1B) that patients with treatment-resistant schizophrenia be treated with clozapine.*

**Clozapine Efficacy and Effectiveness**

Evidence on clozapine comes from multiple RCTs, observational studies (including clinical trials and studies using administrative databases), and meta-analyses. In some instances, the studies were limited to individuals with treatment-resistant schizophrenia, whereas in other studies a formal determination of treatment-resistance was not reported or possible. Nevertheless, most information about clozapine will be of relevance to patients with treatment-resistant schizophrenia because, in current practice, most individuals receive clozapine only after a lack of response to other treatments.

In comparisons of SGAs, the AHRQ report (McDonagh et al. 2017) found that, independent of prior treatment history, clozapine improved core illness symptoms more than other SGAs (except for olanzapine) and was associated with a lower risk of suicide or suicide attempts than olanzapine, quetiapine, and ziprasidone (low SOE). In addition, in treatment-resistant patients, clozapine treatment was associated with a lower rate of treatment discontinuation due to lack of efficacy than the other SGAs that were studied. It is not clear whether rates of overall treatment discontinuation with clozapine may be influenced by the increased frequency of clinical interactions related to the more intensive monitoring with clozapine as compared to other antipsychotic medications.

The AHRQ review drew on several meta-analyses related to treatment-resistant schizophrenia (Ranasinghe and Sin 2014; Samara et al. 2016; Souza et al. 2013); however, some additional studies are also relevant to this guideline statement. A meta-analysis by Siskind and colleagues (Siskind et al. 2016b) had considerable overlap with the meta-analysis of Samara and colleagues (Samara et al. 2016) in terms of the included studies. Despite this, the findings of the two meta-analyses were somewhat different, likely due to differences in the inclusion criteria and analytic approach (Samara and Leucht et al. 2017). Samara and colleagues found few significant differences in outcomes and did not find clozapine to be significantly better than most other drugs in treatment-resistant schizophrenia (Samara et al. 2016). Siskind and colleagues found no difference for clozapine compared to other antipsychotic medications in long-term studies but did find clozapine to be superior to other medications in short-term studies and across all studies in reducing total psychotic symptoms (24 studies, N=1,858; p<0.005) (Siskind et al. 2016b). Similarly, in terms of response to treatment (as reflected by a 20-30% reduction in symptoms), clozapine showed higher rates of response than comparators in short-term studies of treatment-resistant schizophrenia (eight studies, total N=598 for clozapine, 620 for comparators; RR 1.17; 95% CI 1.07 to 2.7; p=0.03; absolute risk reduction 12.48%, 95% CI 7.52 to 17.43; NNT= 9). Again, however, studies that assessed long-term response showed no difference between clozapine and comparators. A greater benefit of clozapine than comparators was also seen when the analysis was limited to non-industry funded trials (six studies, N= 208; RR 1.68, 95% CI 1.20 to 2.35; p=0.002). In a subsequent meta-analysis using data from the same studies, Siskind and colleagues found that 40.1% of treatment-

* 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.
resistant individuals who received clozapine had a response, with a reduction of PANSS scores of 25.8% (22 points on the PANSS) from baseline (Siskind et al. 2017b).

Findings from studies using administrative databases also suggest benefits of treatment with clozapine. For example, a prospective nationwide study conducted over a 7 ½ year period in Sweden (Tiihonen et al. 2017) found significantly reduced rates of rehospitalization with the use of clozapine as compared to no antipsychotic treatment (HR 0.53, 95% CI 0.48 to 0.58). In addition, the reduction in rehospitalization with clozapine was comparable to reductions in rehospitalization with LAI antipsychotic medications whereas other oral formulations of antipsychotic medications had higher risks of rehospitalization. In comparison with oral olanzapine, clozapine had a lower rate of treatment failure (HR 0.58, 95% CI 0.53 to 0.63) that was comparable to the rate of treatment failure with LAI antipsychotic medications (HRs 0.65-0.80). A meta-analysis that examined effects of clozapine on hospital use also found benefits for clozapine (Land et al. 2017). Although the vast majority of studies in the meta-analysis were observational studies, use of clozapine as compared to other antipsychotic medications was associated with a significant decrease in the proportion of individuals who were hospitalized (22 studies, N=44,718; RR 0.74, 95% CI 0.69 to 0.80; p <0.001) although the time to rehospitalization did not differ.

In terms of suicide risk, subjects in the InterSePT trial (Meltzer et al. 2003) who met criteria for treatment-resistant schizophrenia showed benefits of clozapine that were comparable to the benefits seen in the overall sample. For the sample as a whole, clozapine was superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide in high risk patients (HR 0.76, 95% CI 0.58 to 0.97). Fewer clozapine-treated patients in the InterSePT trial attempted suicide (P=0.03), required hospitalizations (P=0.05) or rescue interventions (P=0.01) to prevent suicide, or required concomitant treatment with antidepressants (P=0.01), anxiolytics, or soporifics (P=0.03). Clozapine treated subjects were also less likely to have Clinical Global Impression (CGI)-severity of suicidality scale ratings of “much worse” or “very much worse” (HR 0.78; 95% CI 0.61 to 0.99) than subjects treated with olanzapine.

In terms of mortality risk, a population-based cohort study of 2,370 patients with treatment-resistant schizophrenia found a higher rate of self-harm in individuals treated with non-clozapine antipsychotic medications than for clozapine (HR 1.36, 95% CI: 1.04-1.78) (Wimberley et al. 2017). There was also a higher rate of all-cause mortality in patients not receiving clozapine than for those treated with clozapine (HR 1.88, 95% CI 1.16 to 3.05); however, the comparator group included individuals who were not taking any antipsychotic medication. When the study subjects were limited to those who were adhering to treatment, the higher mortality during treatment with other antipsychotic medications did not reach statistical significance. In the year after clozapine discontinuation, an increase in mortality was observed (HR 2.65, 95% CI 1.47 to 4.78), consistent with benefits of clozapine treatment in reducing overall mortality. Another cohort study also found significant benefits of clozapine on all-cause mortality in individuals with treatment-resistant schizophrenia (adjusted HR 0.61, 95% CI 0.38 to 0.97; p=0.04) (Cho et al. 2019). These findings are also consistent with results of a meta-analysis that showed significantly lower rates of long-term crude mortality in patients who received continuous treatment with clozapine as compared to patients treated with other antipsychotic medications (mortality rate ratio 0.56, 95% CI 0.36 to 0.85; P=0.007) (Vermeulen et al. 2018).
In terms of side effects with clozapine, a network meta-analysis conducted as part of the AHRQ report (McDonagh et al. 2017) showed that clozapine had a higher risk of study withdrawal due to adverse events than some other SGAs (low SOE) but did not show differences in overall rates of adverse events as compared to risperidone (low SOE). In the meta-analysis by Siskind and colleagues (Siskind et al. 2016b), individuals treated with clozapine had a higher likelihood of experiencing sialorrhea ($p<0.001; \text{NNH}=4$), seizures ($p<0.05; \text{NNH}=17$), tachycardia ($p<0.01; \text{NNH}=7$), fever ($p<0.01; \text{NNH}=19$), dizziness ($p<0.01; \text{NNH}=11$), sedation ($p<0.001; \text{NNH}=7$), constipation ($p<0.05; \text{NNH}=12$), and nausea or vomiting ($p<0.05; \text{NNH}=19$) than individuals treated with comparator antipsychotic medications. In the meta-analysis by Leucht and colleagues (Leucht et al. 2013), all cause treatment discontinuation was less likely with clozapine than placebo (OR 0.46, 95% CI 0.32 to 0.65) as were extrapyramidal side effects (OR 0.3, 95% CI 0.17 to 0.62). In contrast, weight gain (SMD 0.65, 95% CI 0.31 to 0.99) and sedation (OR 8.82, 95% CI 4.72 to 15.06) were more likely with clozapine than placebo.

In an Australian national survey of 1,049 people with a diagnosis of schizophrenia or schizoaffective disorder who reported taking any antipsychotic medication (Siskind et al. 2017a), the proportion of individuals with diabetes, obesity, and metabolic syndrome was higher in individuals taking clozapine as compared to other antipsychotic medications (adjusted OR 1.744, 1.899, and 2.300 respectively; $p<0.001$ for each). In addition, clozapine was associated with a greater proportion of individuals with dry or watery mouth (adjusted OR 2.721; $p<0.001$), difficulty swallowing (adjusted OR 1.754; $p<0.01$), constipation (adjusted OR 1.996; $p<0.001$), dizziness/vertigo (adjusted OR 1.571; $p<0.01$), and palpitations (adjusted OR 1.543; $p<0.05$). The proportion of individuals who reported trembling/shaking was significantly less in those treated with clozapine as compared to other antipsychotic agents (adjusted OR 0.581; $p<0.01$).

Other Interventions for Treatment-resistant Schizophrenia

High Doses of Antipsychotic Medication

A limited amount of evidence suggests no benefit from high doses of an antipsychotic medication in individuals who have not responded to typical doses of the medication. A systematic review and meta-analysis by Dold and colleagues (Dold et al. 2015) found 5 trials, which included a total of 348 patients and studied this question with FGAs or SGAs. Dose escalation was not found to confer any benefits, either in terms of study attrition, response rates, or symptoms (as measured by PANSS or BPRS).

Use of Antipsychotic Medications Other than Clozapine

The network analysis conducted as part of the AHRQ review (McDonagh et al. 2017) found that treatment-resistant patients had a small benefit with olanzapine over other older SGAs in core illness symptom improvement and negative symptoms, whereas response rates and all-cause treatment discontinuations were not different. Negative symptoms were also significantly reduced with olanzapine as compared to haloperidol (N=2,207; MD 1.28, 95% CI 0.11 to 2.44) and patients treated with ziprasidone showed better response than those treated with haloperidol (N=120; RR 1.54, 95% CI 1.19 to 2.00).
Augmentation Pharmacotherapy

A number of pharmacotherapies have been studied as augmentation strategies in individuals with treatment-resistant schizophrenia. Evidence has primarily been from small short-term, open-label studies that have yielded mixed findings. Correll and colleagues (Correll et al. 2017b) conducted a systematic search for meta-analyses that addressed the effects of combining an antipsychotic medication with another pharmacotherapy in individuals with schizophrenia. They found 29 meta-analyses that together encompassed 19,833 subjects in 381 trials and that evaluated 42 augmentation strategies. Although 14 of these augmentation therapies showed better outcomes than comparison treatment, the meta-analyses with the highest effect sizes had the lowest quality of included studies, undermining confidence in the benefits of augmentation.

In terms of augmentation of clozapine, Siskind and colleagues (Siskind et al. 2018) conducted a systematic review and meta-analysis of augmentation strategies for individuals with clozapine refractory schizophrenia and found 46 studies of 25 interventions. They noted possible benefits of memantine for negative symptoms and aripiprazole, fluoxetine, and sodium valproate for overall psychotic symptoms but found that many of the studies had a poor study quality and short periods of follow-up, which limited the ability to draw conclusions. Wagner and colleagues (Wagner et al. 2019) conducted a systematic meta-review of 21 meta-analyses that examined strategies for augmenting treatment with clozapine. Although the best evidence was available for combination treatment of clozapine with FGAs or SGAs for psychotic symptoms and for antidepressants for persistent negative symptoms, these authors also concluded that additional high-quality clinical trials are essential before making definitive statements about clozapine augmentation. Furthermore, their findings are consistent with those of Correll and colleagues (Correll et al. 2017b), who did not identify any combination medication strategies with clozapine that led to better outcomes than comparator treatments and found that available studies were of low quality.

Other meta-analyses have also examined the effects of using more than one antipsychotic medication as compared to antipsychotic monotherapy. Galling and colleagues (Galling et al. 2017) found a possible benefit of aripiprazole augmentation in terms of greater improvement in negative symptoms and reductions in prolactin levels and body weight. However, they noted that the apparent benefits of antipsychotic augmentation in reducing total symptoms were no longer seen when the analysis was restricted to double-blind trials of higher quality. A Cochrane review of antipsychotic combination treatments for schizophrenia (Ortiz-Orendain et al. 2017) also found that evidence on combinations of antipsychotic medications was of very low quality. Nevertheless, data from a large nationwide cohort study in Finland suggested that use of two different antipsychotic medications may have some benefits as compared to monotherapy. Tiihonen and colleagues (Tiihonen et al. 2019) studied 62,250 patients with a diagnosis of schizophrenia and compared hospitalization rates within the same individual during periods of antipsychotic monotherapy and periods with use of more than one antipsychotic medication. They found that rehospitalization rates with clozapine were lower than with other monotherapies and that individuals receiving more than one antipsychotic medication had a 7% to 13% lower risk of psychiatric rehospitalization than individuals treated with monotherapy (p<0.001). Use of multiple antipsychotic medications was also associated with a reduction in secondary outcomes (e.g., all-cause...
hospitalization, non-psychiatric hospitalization, mortality). Thus, there is weak and inconsistent evidence suggesting possible benefits of combined treatment with more than one antipsychotic medication, but more research is needed.

On the other hand, augmentation of antipsychotic therapy with an antidepressant medication may be helpful, particularly for patients with negative symptoms or depression. Stroup and colleagues (Stroup et al. 2019) used U.S. Medicaid data on 81,921 adult outpatients aged 18-64 years who had a diagnosis of schizophrenia. The authors employed propensity score matching and weighted Cox proportional hazards regression models to examine the effect of adding an antidepressant, a benzodiazepine, a mood stabilizer, or another antipsychotic medication to existing treatment with an antipsychotic medication. These authors found that the addition of an antidepressant medication was associated with a reduced risk for psychiatric hospitalization or emergency visits. In addition, Helfer and colleagues (Helfer et al. 2016) conducted a systematic review and meta-analysis of the addition of antidepressant medication to antipsychotic treatment. Data from the 82 RCTs that included 3,608 subjects found that antidepressant augmentation was associated with greater reductions in depressive symptoms (SMD -0.25, 95% CI -0.38 to -0.12), negative symptoms (SMD -0.30, 95% CI -0.44 to -0.16), overall symptoms (SMD -0.24, 95% CI -0.39 to -0.09), positive symptoms (SDM -0.17, 95% CI -0.33 to -0.01), quality of life (SMD -0.32, 95% CI -0.57 to -0.06), and responder rate (risk ratio: 1.52, 95% CI 1.29 to 1.78; NNT: 5, 95% CI 4 to 7).

Electroconvulsive Therapy

Some studies have shown evidence for benefits of electroconvulsive therapy (ECT) in combination with antipsychotic medications. Pompili and colleagues (Pompili et al. 2013) conducted a systematic review that included RCTs and observational studies, including case control studies, and concluded that ECT in combination with antipsychotic medications may be helpful for a subgroup of individuals who have treatment resistance, catatonia, aggression, or suicidal behavior, particularly when rapid improvement is needed.

Zheng and colleagues (Zheng et al. 2016) conducted a systematic review and meta-analysis of RCTs comparing antipsychotic medications other than clozapine to antipsychotic medication in combination with ECT in patients with treatment-resistant schizophrenia. In the 11 studies, which included 818 patients, the addition of ECT was associated with greater improvements in symptoms (SMD -0.67; p<0.00001) and greater rates of study-defined response (RR 1.48; p<0.0001; NNT=6), and remission (RR 2.18; p=0.0002; NNT=8) as well as greater rates of headache (p=0.02; NNH=6) and memory impairment (p=0.001; NNH=3).

In terms of ECT augmentation of clozapine in treatment-resistant schizophrenia, Petrides and colleagues (Petrides et al. 2015) conducted a randomized, single-blind, 8-week trial in which patients who had not responded to clozapine alone received a constant dose of clozapine or clozapine plus bilateral ECT (three times per week for 4 weeks and then twice weekly for 4 weeks for 20 total treatments). Fifty percent of the patients treated with ECT plus clozapine experienced a reduction in psychotic symptoms of at least 40% and also achieved a CGI-improvement rating of much improved and a CGI-severity rating of borderline mentally ill or not at all ill. This contrasts with patients who received clozapine but not ECT in the randomized phase of the trial, none of whom showed response by these criteria. When the latter
group of patients received ECT in the unblinded crossover phase of the trial, the rate of response was 47%. Global cognitive outcomes did not differ for the two randomized groups. Lally and colleagues (Lally et al. 2016b) conducted a systematic review and found five trials (four open label studies plus the study of Petrides et al. with a total of 71 subjects) in which the pooled response rate to clozapine plus ECT was 54%. When cohort studies, non-blinded randomized trials, case series, and case reports were considered, the overall response rate for clozapine plus ECT was 76% (83 of 126 patients), even though clozapine doses and serum levels were relatively high (mean serum clozapine level of 772.6 ng/mL at a mean daily dose of 506.9 mg for the 52 patients with an available clozapine level; mean daily dose 412.3 mg for the sample as a whole). Wang and colleagues (Wang et al. 2018b) conducted a systematic review and meta-analysis of RCTs of ECT augmentation of clozapine for clozapine-resistant schizophrenia that included Chinese and non-Chinese studies. Findings from 18 RCTs that included 1,769 subjects showed benefits of adjunctive ECT compared to clozapine alone for symptomatic improvement at post-ECT and endpoint assessments (SMD -0.88, p=0.0001 and SMD -1.44, p<0.00001, respectively). Significant benefits of adjunctive ECT were also seen in study-defined response rates and in remission rates at both assessments (p<0.00001, NNT 3 and 4, respectively, for response and p≤0.0001, NNT 13 and 14, respectively, for remission); however, subjective memory issues and headache were more frequent in the group that received adjunctive ECT (p<0.0001, NNH 4 and p=0.005, NNH 8, respectively).

These studies and meta-analyses suggest a beneficial effect of ECT in combination with antipsychotic medication in individuals with treatment-resistant schizophrenia and clozapine-resistant schizophrenia despite the small number of studies and low quality of observational trials. The increases in reported rates of headache and memory impairment, however, suggest a need to weigh the potential benefits and risks of ECT for the individual patient as compared to the risks of treatment-resistant schizophrenia.

Transcranial Magnetic Stimulation in Treatment-resistant Schizophrenia

Studies have also been done with transcranial magnetic stimulation (TMS) for treatment of hallucinations and for treatment of negative symptoms in individuals with schizophrenia. He and colleagues (He et al. 2017) conducted a meta-analysis of studies published in English or Chinese that studied low (1-Hz) or high (10-Hz) frequency TMS in individuals with schizophrenia. In 13 studies of 1-Hz TMS, auditory hallucinations showed greater improvement with active TMS as compared to sham treatment, but publication bias was noted, and sensitivity analysis also indicated that the meta-analytic finding was unstable and likely to change with additional research. In 7 studies of 10-Hz TMS, there was no effect of active treatment on negative symptoms as compared to sham TMS.

Aleman and colleagues (Aleman et al. 2018) conducted a meta-analysis of studies of TMS applied to the dorsolateral prefrontal cortex as compared to sham TMS for treatment of negative symptoms and found a mean weighted effect size of 0.64 (0.32-0.96, total N=827); however, sham TMS showed a significant improvement of negative symptoms from baseline to post-treatment with a mean weighted effect size of 0.31 (0.09-0.52, total N =333). Interpretation of the findings was also complicated by the use of several different coil placements (i.e., right, left, bilateral) and variability in other stimulation parameters (e.g., frequency, intensity, number of stimuli per session, duration of treatment). A meta-analysis of Dollfus and colleagues (Dollfus et al. 2016) of 13 parallel design trials of TMS for treatment of auditory...
hallucinations in schizophrenia also showed a significant placebo effect, which was greatest with the 45° position coil and was viewed as introducing substantial bias in determining TMS efficacy.

In terms of addition of TMS to clozapine, Wagner and colleagues (Wagner et al. 2019) used data from the rTMS for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial and examined a subgroup of patients who received treatment with clozapine with the addition of active (N=12) or sham (N=14) TMS applied to the left dorsolateral prefrontal cortex for 3 weeks with 5 treatment sessions per week. There was no effect of active TMS on negative symptoms although there was significant benefit of TMS on secondary outcomes (i.e., PANSS positive symptom and general subscales; total PANSS).

These findings on benefits of TMS may change with further research using larger samples and rigorous study designs; however, at present, there is limited evidence for benefits of TMS in reducing either auditory hallucinations or negative symptoms and findings are confounded by significant placebo effects and publication biases.

**Statement 6**

APA recommends (1B) that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*

For individuals with schizophrenia who are at substantial risk for suicide, evidence on the use of clozapine comes from retrospective cohort studies and a large pragmatic, open-label RCT (N=980). Consequently, the strength of research evidence is rated as moderate.

Based on findings from the InterSePT trial (Meltzer et al. 2003), the AHRQ report (McDonagh et al. 2017) concluded that clozapine was superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide in high risk patients (HR 0.76, 95% CI 0.58 to 0.97; moderate SOE). Fewer clozapine-treated patients in the InterSePT trial attempted suicide (P=0.03), required hospitalizations (P=0.05) or rescue interventions (P=0.01) to prevent suicide, or required concomitant treatment with antidepressants (P=0.01), anxiolytics, or soporifics (P=0.03). Although there was not a significant difference in suicide deaths (5 for clozapine and 3 for olanzapine), Kaplan-Meier life-table estimates indicated a significant reduction in the two-year event rate in the clozapine group (p=0.02) with a NNT of 12. Data from other RCTs, in which suicide-related outcomes were reported as adverse events, showed very low event rates and no differences among antipsychotic medications.

One large retrospective study (Kiviniemi et al. 2013) used a nationwide registry to follow-up patients presenting with a first episode of schizophrenia (N=6,987). At 5 years, the risk of suicide in those treated with clozapine was significantly reduced (OR 0.29, 95% CI 0.14 to 0.63) whereas suicide risk in those treated with risperidone, olanzapine, or quetiapine was comparable to the risk with no antipsychotic treatment. Another large nationwide study (N=9,567) of patients newly starting on SGAs found lower rates of suicide attempts in those beginning on clozapine as compared to other drugs studied (Bitter et al. 2013). Suicide attempt rates were 1.1% at one year in those treated with clozapine in contrast to

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* 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.
suicide attempt rates that ranged from 2.1% to 3.7% for other SGAs at one year. The suicide attempt rate with clozapine treatment was also reduced as compared to the 6 months prior to clozapine initiation (2.2% prior to clozapine as compared to 1.1% after clozapine initiation).

For a discussion of the evidence related to the side effects of clozapine, see Appendix C, Statement 5.

Statement 7

APA suggests (2C) that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments. *

Evidence for the use of clozapine for individuals with substantial aggressive behavior is limited and the strength of research evidence is rated as low.

A systematic review on pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders found 92 articles with sufficient methodological information to evaluate although none were at low risk of bias (Victoroff et al. 2014). They found two studies (one RCT, N=157; one open-label, N=44) showing that, in inpatients with schizophrenia spectrum disorders, clozapine was superior to haloperidol in reducing scores on the Overt Aggression Scale (Ratey et al 1993; Conley et al. 2003). Another RCT conducted in physically assaultive inpatients (N=100) also found clozapine to be superior to haloperidol or olanzapine in reducing scores on the Overt Aggression Scale (Krakowski et al. 2006; Krakowski et al. 2008). In reducing hostility (as measured by PANSS or BPRS hostility items), four RCTs (three in inpatients, one in outpatients) reported superiority of clozapine as compared to FGAs. Two of these studies (N=48 and N=151) compared clozapine to chlorpromazine (Claghorn et al. 1987; Niskanen et al. 1974) whereas two studies (N=167 and N=71) compared clozapine to haloperidol (Citrome et al. 2001; Kane et al. 2001). These findings support the opinions of many experts in viewing clozapine as beneficial in those at substantial risk of aggressive behaviors.

Nevertheless, additional evidence from well-designed clinical trials is needed. For a discussion of the evidence related to the side effects of clozapine, see Appendix C, Statement 5.

Statement 8

APA recommends (1A) that patients with schizophrenia whose symptoms have improved with antipsychotic medication continue to be treated with an antipsychotic medication. *

Evidence in support of this statement is primarily based on the evidence for antipsychotic efficacy in improving symptoms and quality of life as well as promoting functioning (See Appendix C, Guideline Statement 4). Thus, the strength of research evidence is rated as high.

Additional evidence supporting this statement comes from registry database studies and from discontinuation studies. For example, in a nationwide prospective registry study (N=6,987) with a 5-year follow-up of individuals with first-onset schizophrenia (Kiviniemi et al. 2013), there was a significant

* 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.
decrease in all-cause mortality in individuals taking SGAs as compared to individuals who were not taking antipsychotic medication (OR 0.69; p=0.005). Another nationwide study (N=8,719) using prospectively collected registry data found that the lowest rates of rehospitalization or death occurred in individuals who received continuing treatment with an antipsychotic medication for up to 16.4 years (Tiihonen et al. 2018). Individuals who discontinued antipsychotic medication had a risk of death that was 174% higher than that in continuous users of antipsychotic medications (HR 2.74, 95% CI 1.09 to 6.89), whereas the risk of death was 214% higher (HR 3.14, 95% CI 1.29 to 7.68) in non-users of antipsychotic medications as compared to continuous users. Rates of treatment failure, which included rehospitalization as well as death, were also lower in individuals who received continuous treatment with an antipsychotic medication. More specifically, 38% of those who discontinued treatment experienced treatment failure as compared to a matched group of continuous users of an antipsychotic medication, in which the rate of treatment failure was 29.3%. For non-users of antipsychotic medication, treatment failure occurred in 56.5% as compared to 34.3% of a matched group of continuous antipsychotic medication users.

Based on 10 RCTs (total N=776) with mean study duration of 18.6 ± 5.97 months, a meta-analysis of discontinuation studies (Kishi et al. 2018) concluded that relapse rates were lower in individuals with schizophrenia who continued treatment with an antipsychotic medication as compared to those who discontinued treatment (RR 0.47; 95% CI 0.35 to 0.62; p<0.00001; I²=31%; NNT=3). An additional meta-analysis (Thompson et al. 2018), using somewhat different inclusion and exclusion criteria for studies, also found that relapse rates were lower in individuals who received maintenance treatment (19%; 95% CIs: 0.05% to 37%; N=230) as compared to those who stopped the antipsychotic medication (53%; 95% CIs: 39% to 68%; N=290). Although caution may be needed in interpreting these results due to methodological considerations (Moncrieff and Steingard 2019), the findings align with expert opinion on the benefits of maintenance treatment with an antipsychotic medication (Goff et al. 2017).

Statement 9

APA suggests (2B) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.**

Evidence in support of this statement includes the evidence described for antipsychotic efficacy (as described in Appendix C, Guideline Statement 4) and the evidence for remaining on antipsychotic treatment (as described in Appendix C, Guideline Statement 8). Additional evidence that specifically addresses this guideline statement comes from randomized trials of a change in antipsychotic medication. Based on these studies, the strength of research evidence is rated as moderate.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study provided important findings on medication changes (Essock et al. 2006). At the time of randomization, some individuals happened to be randomly assigned to a medication that they were already taking whereas other individuals were assigned to a different antipsychotic medication. Individuals who were assigned to change to a different

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antipsychotic medication (N=269) had an earlier time to all-cause treatment discontinuation than those
assigned to continue on the same antipsychotic medication (N=129; Cox proportional HR 0.69; p=0.007).
Although a change from olanzapine to a different antipsychotic medication was beneficial in terms of
weight gain, there were no other differences in outcome measures for individuals who switched
medications as compared to those who stayed on the same treatment (Rosenheck et al. 2009).

Additional evidence comes from an RCT aimed at reducing the metabolic risk of antipsychotic treatment
by changing medication from olanzapine, quetiapine, or risperidone to aripiprazole (Stroup et al. 2011).
Individuals were followed for 24 weeks after being assigned to continue on their current medication
(N=106) or to switch to aripiprazole (N=109). Although the two groups did not differ in the proportion of
individuals with medication efficacy (as measured by the PANSS total score or change in CGI-severity
score), individuals who switched medication were more likely to stop medication (43.9% vs 24.5%;
p=0.0019) and treatment discontinuation occurred earlier in those who switched medication as
compared to those who did not (HR 0.456, 95% CI 0.285 to 0.728; p=0.0010). However, modest but
statistically significant changes did occur in weight, serum non-HDL-C, and serum triglycerides in
individuals who switched to olanzapine as compared to those who stayed on olanzapine, quetiapine, or
risperidone.

Together, these findings suggest that changes in antipsychotic medications may be appropriate to
address significant side effects such as weight or metabolic considerations but that switching
medications may also confer an increased risk of medication discontinuation with associated risks of
increased relapse and increased mortality.

Statement 10

APA recommends (1C) that patients who have acute dystonia associated with antipsychotic therapy
be treated with an anticholinergic medication.

This recommendation is based on expert opinion and is supported by studies of the prophylactic use of
anticholinergic medications to reduce the risk of acute dystonia in the initial phases of antipsychotic
therapy. The strength of research evidence for this guideline statement is rated as low.

No studies were found that specifically examined the treatment of acute dystonia with anticholinergic
medications in a randomized or controlled manner although intramuscular administration of an
anticholinergic agent is widely viewed as the treatment of choice for acute dystonia associated with
antipsychotic therapy (Stanilla and Simpson 2017).

Information on the use of anticholinergic medications to prevent acute dystonia associated with
antipsychotic therapy comes from a review of nine studies (Arana et al. 1988) of which four were
randomized, blinded trials (total N=232), two were open trials (total N=856), and three were
retrospective studies (total N=278). Based on data from all of these studies, prophylactic use of an
anticholinergic medication was associated with 1.9-fold reduction in risk of acute dystonia (14.8%
without prophylaxis versus 7.7% with prophylaxis). In patients who received a high potency
antipsychotic agent (e.g., haloperidol), the benefits of prophylactic anticholinergic medication were even
more pronounced (5.4-fold reduction in risk; 46.8% without prophylaxis versus 8.7% with prophylaxis). A
subsequent study of consecutive psychiatric admissions (N=646) showed a lower rate of acute dystonia in patients who received anticholinergic prophylaxis (8.5% without anticholinergic prophylaxis versus 2.8% with anticholinergic prophylaxis) and rates of acute dystonia were greater in individuals treated with a high potency antipsychotic agent (Spina et al. 1993). A small double-blind RCT (N=29) showed a decrease in acute dystonia associated with antipsychotic therapy in patients who received benztropine as compared with placebo, but the results did not reach statistical significance (Goff et al. 1991). These studies suggest therapeutic effects of anticholinergic medications in acute dystonia associated with antipsychotic therapy and, although they were conducted in patients who received FGAs, they likely would also apply to acute dystonia when it occurs with use of SGAs.

Statement 11

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.

This statement is based on expert opinion and, consequently, the strength of research evidence is rated as low.

Knowledge of pharmacology and pharmacokinetics suggests that side effects such as parkinsonism may be diminished by reducing the dose of a medication or changing to a medication with a different side effect profile and a lesser propensity for treatment-related parkinsonism. Clinical experience also suggests that an anticholinergic medication can be used to treat antipsychotic-associated parkinsonism (Stanilla and Simpson 2017). A good quality systematic review assessed the use of anticholinergic medication as compared to placebo for parkinsonism associated with antipsychotic therapy (Dickenson et al. 2017). Although many studies of anticholinergic treatment for parkinsonism were conducted decades ago and suggested benefits of anticholinergics, few of these studies met the systematic review’s inclusion criteria. In addition, sample sizes in the two included studies were small and no definitive conclusions could be drawn from the systematic review.

Statement 12

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.

This statement is based on expert opinion and, consequently, the strength of research evidence is rated as low.

Knowledge of pharmacology and pharmacokinetics suggests that side effects such as akathisia may be diminished by reducing the dose of a medication or changing to a medication with a different side effect profile and a lesser propensity for treatment-related akathisia. The suggestion to use a benzodiazepine or beta-adrenergic blocking agent to treat antipsychotic-associated parkinsonism is also based on expert opinion and clinical experience (Stanilla and Simpson, 2017). A good quality systematic review identified some benefits of benzodiazepines for akathisia associated with antipsychotic therapy (Lima et al. 2002), but only two studies (total N=27) met the inclusion criteria. Another good quality systematic review
assessed the use of beta-adrenergic blocking agents in akathisia and also found insufficient evidence to
draw conclusions about therapeutic benefits (three RCTs, total N=51; Lima et al. 2004). In addition, no
reliable evidence was found to support or refute the use of anticholinergic agents as compared to
placebo for akathisia associated with antipsychotic therapy (Rathbone and Soares-Weiser et al. 2006).
The literature search did not identify well-designed trials published after these systematic reviews that
shed additional light on any of these treatment approaches.

Statement 13

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 transporter2 (VMAT2) (e.g., deutetrabenazine, tetrabenazine, valbenazine).

This statement is based on information from a good-quality systematic review (Solmi et al. 2018c) on
deutetrabenazine and valbenazine treatment whereas information on tetrabenazine comes from less
robust clinical trials. The strength of research evidence for this guideline statement is rated as moderate.

For deutetrabenazine, data was available from two double-blind, placebo-controlled RCTs (Anderson et
al. 2017; Fernandez et al. 2017) that enrolled subjects with moderate to severe tardive dyskinesia. Each
trial lasted 12 weeks and doses of deutetrabenazine were 12-48 mg/day. Treatment with
deutetrabenazine was associated with a significant decrease in total Abnormal Involuntary Movement
Scale (AIMS) scores (N=413; SMD -0.40, 95% CI -0.19 to -0.62, p<0.001; weighted mean difference
(WMD) -1.44, 95% CI -0.67 to -2.19, p<0.001) and significantly greater rates of response (defined as an
AIMS score reduction of at least 50%; RR 2.13, 95% CI 1.10 to 4.12, p=0.024; NNT=7, 95% CI 3 to 333,
p=0.046; Solmi et al. 2018c). The rate of treatment response increased with treatment duration during
the open-label extension phase of the study (Hauser et al. 2019). Deutetrabenazine was well-tolerated
with trial completion rates and rates of adverse effects that were similar to rates with placebo (Solmi et
al. 2018c).

For valbenazine, data was available from four double-blind, placebo-controlled trials (total N=488) of
two to six weeks each using valbenazine doses of 12.5-100 mg/day in individuals with moderate to
severe tardive dyskinesia (Citrome et al. 2017b; Correll et al. 2017a; Factor et al. 2017; Hauser et al.
2017; Josiassen et al. 2017; Kane et al. 2017; O’Brien et al. 2015). Treatment with valbenazine was
associated with a significant decrease in total AIMS scores (N=421; SMD -0.58, 95% CI -0.26 to -0.91,
p<0.001; WMD -2.07, 95% CI -1.08 to -3.05, p<0.001) and significantly greater rates of response (RR
3.05, 95% CI 1.81 to 5.11, p<0.001; NNT 4, 95% CI 3 to 6, p<0.001; Solmi et al. 2018c). With valbenazine,
as with deutetrabenazine, the rate of treatment response increased with treatment duration during the
open label extension phase of the study (Factor et al. 2017). Furthermore, in the randomized KINETC3
study, a dose-response relationship was observed with greater benefit at doses of 80 mg/day as
compared to 40 mg/day (Hauser et al. 2017). Valbenazine was well-tolerated with trial completion rates
and rates of adverse effects that were similar to rates with placebo (Solmi et al. 2018c).

For tetrabenazine, prospective placebo-controlled data is more limited and includes a single-blind trial
of 20 subjects (Ondo et al. 1999), a double-blind crossover trial of six subjects (Godwin-Austen and Clark,
benefits of tetrabenazine were seen at doses of up to 150 mg/day, the quality of evidence is not sufficient to draw robust conclusions or conduct meta-analyses (Leung and Breden 2011; Solmi et al. 2018c). Adverse effects that were more frequent with tetrabenazine than placebo included drowsiness, sedation/somnolence, parkinsonism, insomnia, anxiety, depression, and akathisia.

Although this statement specifically relates to the use of reversible inhibitor of the vesicular monoamine transporter2 (VMAT2) (e.g., deutetabenazine, tetrabenazine, valbenazine), the guideline writing group also reviewed systematic reviews of other possible treatments for tardive dyskinesia. This evidence is shown in Table C-2.

Table C-2. Other systematic reviews of treatments for tardive dyskinesia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Citation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic agents</td>
<td>Bergman and Soares-Weiser 2018</td>
<td>Two trials (total N=30) of very low-quality evidence</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Bergman et al. 2018a</td>
<td>Four trials (total N=75) of very low-quality evidence showed no clinically significant difference relative to placebo</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Soares-Weiser and Rathbone 2011</td>
<td>No studies met inclusion criteria</td>
</tr>
<tr>
<td>Cessation or reduction of antipsychotic</td>
<td>Bergman et al. 2018b</td>
<td>Two trials (total N=17) with very low_quality evidence</td>
</tr>
<tr>
<td>Change to clozapine</td>
<td>Mentzel et al. 2018</td>
<td>Four trials (total N=48) with subjects who had clinically significant tardive dyskinesia showed improvement with a change to clozapine (standardized mean change −2.56, 95% CI −4.85 to −0.28, p=0.02), which is consistent with observational data (Pinninti et al. 2015; Lieberman et al. 1991; Naber et al. 1989).</td>
</tr>
<tr>
<td>Cholinergic medication</td>
<td>Tammenmaa-Aho et al. 2018</td>
<td>Low quality evidence showed no clinically important improvement in tardive dyskinesia symptoms (four trials; N=27) or effect on deterioration of tardive dyskinesia symptoms (eight trials; N=147) when compared with placebo.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Reference</td>
<td>Evidence Summary</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid agonists</td>
<td>Alabed et al. 2011</td>
<td>Low quality evidence showed no clinically important improvement in tardive dyskinesia symptoms (three trials; N=108) and a greater rate of side effects and attrition was suggested.</td>
</tr>
<tr>
<td>Ginkgo biloba extract</td>
<td>Soares-Weiser et al. 2018b</td>
<td>One trial (N=157) showed benefit compared with placebo (RR 0.88, 95% CI 0.81 to 0.96) in a moderate quality study, but requires replication.</td>
</tr>
<tr>
<td>Non-antipsychotic catecholaminergic drugs</td>
<td>El-Sayeh et al. 2018</td>
<td>10 trials (N=261) with very low-quality evidence and one to two trials per therapeutic comparison</td>
</tr>
<tr>
<td>Vitamin B6 (Pyridoxal 5 phosphate)</td>
<td>Adelufosi et al. 2015</td>
<td>Three trials (total N=80) of inpatients followed for nine to 26 weeks showed significant improvement in tardive dyskinesia symptoms when compared with placebo but evidence was of low quality, with wide confidence intervals.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Soares-Weiser et al. 2018a</td>
<td>13 trials (total N=478) showed possible blunting of additional deterioration but no clear difference when compared with placebo in terms of clinically important improvement</td>
</tr>
<tr>
<td>Miscellaneous agents, including branched chain amino acids, buspirone, dihydrogenated ergot alkaloids, estrogen, gamma-linolenic acid, insulin, isocarboxazid, lithium, melatonin, pemoline, promethazine, ritanserin, and selegiline</td>
<td>Soares-Weiser et al. 2018b</td>
<td>Inconclusive low to very low-quality evidence from one to two short-term trials and a total N of 10 to 52 for each medication</td>
</tr>
</tbody>
</table>

Amantadine has also been mentioned in the literature as a treatment for tardive dyskinesia but evidence for its use is extremely limited. One randomized double-blinded crossover trial (Angus et al. 1997) included only 16 patients and had significant attrition. Another randomized, double-blinded
crossover trial (Pappa et al. 2010) also had a small sample (N=22) and the period of treatment was only two weeks. Thus, data from these trials are insufficient to support use of amantadine for treatment of tardive dyskinesia.

Psychosocial Interventions

Statement 14

**APA recommends (1B) that patients with schizophrenia be treated with cognitive-behavioral therapy (CBT).***

Evidence in support of this statement comes from multiple RCTs and meta-analyses as described in the AHRQ review (McDonagh et al. 2017). The strength of the research evidence is rated as moderate based on the evidence of CBT benefits for core illness symptoms and short-term functioning.

In terms of overall symptoms, the AHRQ report relied primarily on a systematic review of 34 RCTs (Jauhar et al. 2014) that found CBT for individuals with psychosis (CBTp) to be more effective than usual care at improving overall symptoms based on symptom-based rating scales such as the PANSS and BPRS (SMD -0.33, 95% CI -0.47 to -0.19; I²=68%; moderate SOE). The effect was less pronounced but remained significant (95% CI -0.27 to -0.03) when the analysis was restricted to trials with blinded outcome assessments. Because this review did not conduct stratified analysis by format, it is not possible to tell whether distinctions in outcome exist for individual as compared to group CBTp. Although the included studies ranged in duration from 8 weeks to 5 years, analysis of shorter as compared to longer durations of treatment was not conducted, limiting the ability to determine whether more prolonged treatment is able to maintain shorter term treatment gains. For negative symptoms, there was no meaningful difference noted between CBTp and usual care based on data from two systematic reviews (Jauhar et al. 2014; Velthorst et al. 2015) (low SOE).

The AHRQ report (McDonagh et al. 2017) also found CBTp to be associated with improvements in global function in the short-term (≤6 months since CBTp initiation) as measured using the Global Assessment of Functioning (GAF) scale (6 trials; MD 5.35, 95% CI 1.05 to 9.65; I²=77%). Removing the one study that used group CBTp from the analysis strengthened the effect and eliminated statistical heterogeneity. In one study that focused on global function (van der Gaag et al. 2011)) a higher proportion of CBTp patients had normal functioning after six months of treatment as compared to patients who received usual care (28% vs. 14%; RR 2.21, 95% CI 1.25 to 3.93). Short-term improvements in social and/or occupational function (as measured by Social and Occupational Functioning Assessment Scale (SOFAS)) were also noted based on a pooled analysis from two studies (MD 9.11, 95% CI 6.31 to 11.91; low SOE).

In one trial, significantly more participants in the CBTp group achieved a normal level of function (as measured by Social Functioning Scale (SFS) score) as compared to usual care (RR 2.21, 95% CI 1.25 to 3.93). Benefits of CBT-p on global, social and occupational function were not maintained for more than six months after treatment cessation (low SOE). CBTp also improved quality of life more than usual care in the short-term but not with longer periods of follow-up (low SOE).

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Harms of treatment were rarely reported in studies of CBTp and the AHRQ report notes that the evidence is insufficient to draw any conclusions (McDonagh et al. 2017).

Statement 15

**APA recommends (1B) that patients with schizophrenia receive psychoeducation.**

Evidence in support of this statement comes from a good-quality systematic review as described in the AHRQ report (McDonagh et al. 2017). The strength of the research evidence is rated as moderate based on the evidence of psychoeducation benefits on relapse rates.

The 10 RCTs (total N=1,125) of psychoeducation included in the systematic review (Pekkala and Merinder 2002) varied in length (with duration of follow-up as long as 5 years), included diverse interventions, and used individual and group techniques. Although most of the studies included stabilized outpatients and were conducted in North America and northern Europe, many studies contained some individuals with a diagnosis other than schizophrenia. Based on the data from 6 trials, psychoeducation had a greater effect than usual care on relapse rates (with or without readmission) at 9 to 18 months of follow-up (RR 0.80, 95% CI 0.70 to 0.92; moderate SOE). Psychoeducation was also superior to usual care in terms of global functional outcomes at 1 year of follow-up (3 RCTs; MD -5.23, 95% CI -8.76 to -1.71; low SOE).

In terms of potential harms, few studies reported adverse outcomes. Nevertheless, with psychoeducation as compared to usual care no differences were observed in the number of deaths, which were small in both groups, and rates of all-cause study drop-out were also comparable between study groups (McDonagh et al. 2017).

Statement 16

**APA recommends (1B) that patients with schizophrenia receive supported employment services.**

Evidence in support of this statement comes from one study comparing supported employment to usual care and an RCT and meta-analysis comparing supported employment to other vocational interventions as described in the AHRQ report (McDonagh et al. 2017). The strength of the research evidence is rated as moderate based on the evidence of benefits for supported employment on obtaining competitive work.

The AHRQ review (McDonagh et al. 2017) found that supported employment, using the individual placement and support (IPS) model, results in better employment outcomes than usual care with 2 years of follow-up. Patients receiving IPS in one fair-quality trial (N=204) were significantly more likely to obtain competitive work than those receiving usual care (75% vs. 27.5%, p=0.001; Mueser et al. 2004). They were also more likely to obtain any form of paid work than those receiving usual care (73.9% vs. 53.6%). A large RCT (N=1,273), with both usual care and vocational training comparisons, showed similar benefits of IPS (55% vs 34%, p<0.001 overall; and 22% vs. 12%, p< 0.001 in the subgroup of study

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subjects with schizophrenia) (Cook et al. 2005). These findings are consistent with findings of a good quality systematic review of 14 RCTs (N=2,265) in which other vocational training interventions were used as controls (Kinoshita et al. 2013). Together, these studies provide a moderate SOE for benefits of supported employment using IPS. Although associated with a lower SOE, supported employment also showed benefits in terms of working more than 20 hours per week (13% vs. 34%, p=0.00), having more weeks of employment overall (24 more weeks competitive and 11 more weeks any employment, p<0.001), and longer tenure per individual job (4 weeks, p=0.048) than those in either usual care, other vocational interventions, or both. Patients receiving IPS also reported earning more money than those in usual care ($2,078/month vs $617.59/month, p<0.001).

Several other meta-analyses of supported employment using somewhat different analytic methods and different inclusion and exclusion criteria than the AHRQ review found similar benefits of supported employment using the IPS approach (Frederick and VanderWeele 2019; Suijkerbuijk et al. 2017).

Statement 17

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 breakdown (e.g., homelessness; legal difficulties, including imprisonment).*

This recommendation is based on information from the AHRQ review (McDonagh et al. 2017), which used a good quality systematic review (14 RCTs; N=2,281) as a primary source (Marshall and Lockwood 2000) and also considered one additional RCT (N=118; Systema et al. 2007). The strength of research evidence for this guideline statement is rated as moderate based on the moderate SOE found for multiple key outcomes.

The AHRQ review (McDonagh et al. 2017) focused on assertive community treatment (ACT) alone as compared to usual care and did not include a recent review in which evidence for ACT was combined with evidence for intensive case management. Significant variability was noted in study populations with a range of ages, demographic characteristics, diagnoses, and eligibility criteria (e.g., frequent or recent hospitalization, other risk factors for reduced continuity of care). In addition, the degree of fidelity to ACT principles was often unclear, which may influence effectiveness.

Individuals who received ACT were less likely to discontinue treatment and be lost to follow-up than individuals who received usual care (12 trials; OR 0.51, 95% CI 0.41 to 0.63; moderate SOE). They were also less likely to be admitted to a hospital compared to individuals who received usual care (six RCTs; OR 0.59, 95% CI 0.41 to 0.85; I²=73%), and many of the reported studies also showed a decrease in the number of days in the hospital. Furthermore, individuals who received ACT were less likely to be unemployed (three trials; OR 0.46, 95% CI 0.21 to 0.99; I²=34%), homeless (four trials; OR 0.20, 95% CI 0.09 to 0.47; I²=52%), or living non-independently (four trials; OR 0.52, 95% CI 0.35 to 0.79; I²=0%) compared with usual care (moderate SOE). Core illness symptoms also improved with ACT, but the degree of improvement was comparable to that in the usual care group (three trials, N=255; MD -0.14, 0.14).

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95% CI -0.36 to 0.08; moderate SOE). As compared to usual care, there was no significant difference in social function (pooled analysis of 3 studies; MD 0.03, 95% CI -0.28 to 0.34; low SOE) and no significant differences in arrests (two trials, total N=604; OR 1.17, 95% CI 0.60 to 2.29; I²=0%), imprisonment (four trials, total N=471; OR 1.19, 95% CI 0.70 to 2.01; I²=27%), or police contacts (two trials, total N=149; OR 0.76, 95% CI 0.32 to 1.79; I²=84%) with ACT (low SOE). Findings from the additional RCT were generally consistent with the meta-analytic results. Only two trials reported information on quality of life, with one finding a small but statistically significant difference and the other showing no difference.

In individuals with co-occurring schizophrenia and a substance use disorder, one good-quality systematic review of 32 trials (N=3,165) examined differences between integrated ACT and usual care (Hunt et al. 2013). For most outcomes of interest, only one or two of the studies from the systematic review contributed relevant data; however, these limited data showed no differences between integrated ACT and usual care for substance use, treatment discontinuation, function, or mortality through follow-up durations of up to 36 months.

Statement 18

APA recommends (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a team-based, multicomponent program.*

This recommendation is based on evidence from four clinical trials as presented in the AHRQ review (McDonagh et al. 2017) as well as an additional study (Anderson et al. 2018) that showed reduced mortality at two years for those who had participated in an early intervention program. The strength of research evidence for this statement is rated as moderate based on the moderate SOE found for multiple key outcomes.

Pooled results from studies of individuals with a first episode of psychosis (McDonagh et al. 2017) found that up to two years of treatment with a team-based, multicomponent intervention was associated with higher global functioning based on GAF and Global Assessment Scale scores (three RCTs; WMD 3.88, 95% CI 0.91 to 6.85; moderate SOE), significantly more people working or in school (three RCTs; RR 1.22, 95% CI 1.01 to 1.47; moderate SOE), significantly higher ratings of quality of life (two RCTs, effect size 0.84, 95% CI 0.14 to 1.55; moderate SOE) and a greater rate of retention in treatment (RR 1.27, 95% CI 1.16 to 1.38; Cochran Q=0.03, degrees of freedom=1) as compared to usual care. Team-based, multicomponent program participants were also less likely to relapse compared with those in usual care based on two RCTs (two RCTs; RR 0.64, 95% CI 0.52 to 0.79; moderate SOE). These treatment effects were not sustained and had generally dissipated by 5 years after treatment discontinuation. In addition, as compared to usual care, there were no significant effects of multicomponent treatment programs on housing status (two RCTs; low SOE), self-harm (N=506; RR 0.93, CI 0.06 to 14.81), or total PANSS scores (three RCTs; WMD -2.53, 95% CI -5.45 to 0.39; low SOE).

One study (Bertelsen et al. 2007; Nordentoft et al. 2002; Secher et al. 2015) found no differences in rates of accidental death (RR 0.31, 95% CI 0.01 to 7.59) or unexplained death (RR 0.31, 95% CI 0.01 to

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at two years and no difference in mortality at 10 year follow-up (RR 0.92, 95% CI 0.45 to 1.88) between individuals who received a team-based, multicomponent intervention as compared to usual care. In contrast, in an early intervention program for psychosis in Ontario Canada (Anderson et al. 2018), rates of self-harm behavior (HR 0.86, 95% CI 0.18 to 4.24) and suicide (HR 0.73, 95% CI 0.29 to 1.80) did not differ during the initial 2 years after enrollment as compared to usual care but rates of all-cause mortality were lower in the multicomponent intervention group (HR 0.24, 95% CI 0.11 to 0.53; absolute risk reduction 2.5%; NNT=40). As compared to those who received usual care, individuals in the multicomponent program also saw a psychiatrist more rapidly (user median days=13, compared with nonuser median days=78), were more likely to have contact with a psychiatrist (HR 6.05, 95% CI 5.30 to 6.91), and were more likely to be hospitalized (HR 1.42, 95% CI 1.18 to 1.71), but were less likely to have emergency department visits (HR 0.71, 95% CI 0.60 to 0.83) or primary care contacts (HR 0.46, 95% CI 0.41 to 0.52).

Statement 19

APA suggests (2C) that patients with schizophrenia receive cognitive remediation.*

This guideline statement is based on evidence provided by two good-quality systematic reviews (57 studies, total N=2,885; Cella et al. 2017; Wykes et al. 2011), one good-quality trial (N=90; Deste et al. 2015; Vita et al. 2011) and three fair-quality trials (N=56 to 156; Farreny et al. 2012; Mueller et al. 2015; Twamley et al. 2012). The strength of research evidence for this statement is rated as low based on the low SOE found for the majority of outcomes.

Studies included in the AHRQ review (McDonagh et al. 2017) used standard cognitive remediation principles (Saperstein and Medalia 2012) and usual care control comparisons but other population and study characteristics varied (e.g., population demographics, treatment setting, individual versus group format, drill and practice versus drill plus strategy methodology, sessions per week, treatment duration, follow-up duration, extent of treatment fidelity, baseline symptom severity, computerized versus non-computerized content delivery, presence of active comparator condition).

Overall, as compared to usual care, use of cognitive remediation for 15 to 16 weeks of treatment was associated with small positive effects on core illness symptoms (two trials, N=153; SMD -0.62, 95% CI-1.01 to -0.24; low SOE), but effects were inconsistent among the studies and symptom improvement was not sustained following treatment removal (eight RCTs; effect size 0.17, 95% CI -0.03 to 0.48).

Cognitive remediation as compared to usual care was also associated with improvements in negative symptoms (one systematic review of 18 RCTs; effect size -0.36, 95% CI -0.52 to -0.20; moderate SOE) as well as small positive effects on social, occupational, and global function (six RCTs; effect sizes of 0.16 to 0.40; low SOE). Effects of intervention on cognitive functioning were outside of the scope of the AHRQ review but some evidence suggests that improved cognitive function can result from treatment with cognitive remediation with indirect benefits for global function (Harvey et al. 2018). Only one study

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reported on health-related quality of life and study limitations preclude drawing conclusions on this outcome.

Treatment with cognitive remediation did not differ from usual care in terms of rates of treatment discontinuation (McDonagh et al. 2017). Cognitive remediation also seems to be acceptable to individuals who receive treatment in clinical settings as compared to research settings (Medalia et al. 2019).

**Statement 20**

APA suggests (2C) that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*

This guideline statement is based on evidence provided by a fair quality systematic review (13 studies; total N=1,404; Zou et al. 2013) and one additional fair quality study (N=210; Hasson-Ohayon et al. 2007) as described in the AHRQ review (McDonagh et al. 2017) as well as a meta-analysis of person-oriented recovery approaches (seven RCTs, N=1,739; Thomas et al. 2018). The strength of research evidence for this statement is rated as low based on the low SOE found for the majority of outcomes in the AHRQ review and a significant risk of bias (consistent with a low SOE) for most of the studies in the meta-analysis of person-oriented recovery approaches.

For illness self-management training and for recovery-focused interventions, interpretation of the evidence can be challenging because of the degree of heterogeneity in the content and format of the interventions. For example, illness self-management training programs are designed to improve knowledge, management of symptoms, and social and occupational functioning, with a primary goal of reducing the risk of relapse by focusing on medication management, recognizing signs or relapse, and developing a relapse prevention plan and coping skills for persistent symptoms (McDonagh et al. 2017; Substance Abuse and Mental Health Services Administration 2010). Recovery-focused interventions can include similar approaches but are primarily focused on supporting a recovery-oriented vision that strives for community integration in the context of individual goals, needs, and strengths (Le Boutillier et al. 2011; Thomas et al. 2018). Activities of recovery-focused interventions incorporate opportunities for participants to share experiences and receive support as well as practicing strategies for success in illness self-management. With illness self-management, the interventions were typically administered in a group format whereas recovery-focused interventions included a mix of group and individual formats as well as a mix of peer- and professional-led activities. Both illness self-management and recovery-focused interventions had significant variations in session content, duration, and number.

In terms of outcomes with illness self-management, the AHRQ review (McDonagh et al. 2017) noted a reduction in core illness symptom severity based on the BPRS (five RCTs; pooled WMD -4.19, 95% CI -5.84 to -2.54; moderate SOE) and a reduced likelihood of relapse with completion of 10 or more self-management sessions (OR 0.41, 95% CI 0.21-0.79; low SOE). Effects of intervention were reduced if low

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* 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.
fidelity treatment was given or if fewer self-management sessions were completed. No significant effect of illness self-management was noted for negative symptoms (low SOE).

With recovery-focused interventions (Thomas et al. 2018), individuals in the intervention group showed a modest improvement in person-oriented recovery, empowerment, and hope immediately after the intervention (effect size 0.24, 95% CI 0.04, 0.44) and at follow-up (effect size 0.21, 95% CI 0.06, 0.35). Moderator analysis suggested that the greatest improvement was seen when mental health professionals and peer providers collaborated in treatment delivery.

**Statement 21**

APA suggests (2C) that patients with schizophrenia be treated with supportive psychotherapy.*

This guideline statement is based on studies that compared supportive psychotherapy to usual care (total N=822) in one good quality systematic review (Buckley et al. 2015) as described in the AHRQ review (McDonagh et al. 2017). The strength of research evidence for this statement is rated as low based on the low SOE found for study outcomes in the AHRQ review.

The studies in the systematic review (Buckley et al. 2015) were primarily aimed at helping patients with coping abilities and maintaining levels of functioning. In other respects, there was significant variation in measured outcomes, study design (e.g., setting, treatment duration, treatment frequency, follow-up duration), and demographics of the study population (e.g., age, illness duration, symptom severity at baseline). In addition, most of the included studies had some risk of bias.

The AHRQ review (McDonagh et al. 2017) found no difference in global or social function based on two studies, but study results were not able to be pooled for analysis. Four RCTs reported information on study attrition and no significant difference was noted between supportive psychotherapy and usual care (N=354; RR 0.86, 95% CI 0.53 to 1.40; low SOE). For other outcomes, evidence was only available from a single study and sample sizes were small making it difficult to draw reliable conclusions.

**Statement 22**

APA suggests (2B) that patients with schizophrenia who have ongoing contact with family receive family interventions.*

This guideline statement is based on one fair quality systematic review (27 non-Chinese studies, total N=2,297; Pharoah et al. 2010) and six additional studies (total N=562; Barrowclough et al. 1999; Dyck et al. 2000; Garety et al. 2008; Kopelowicz et al. 2012; Mayoral et al. 2015; Sellwood et al. 2001; Sellwood et al. 2007; Valencia et al. 2007) as described in the AHRQ review (McDonagh et al. 2017). Because most family interventions are aimed at reducing relapse, the strength of research evidence for this statement is rated as moderate based on the moderate SOE found for relapse in the AHRQ review with medium-term follow-up, although other outcomes had a low SOE.

* 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.
The studies of family intervention described in the AHRQ review (McDonagh et al. 2017) had significant variation in content and methods of the delivered intervention (e.g., psychoeducation, motivational interviewing, behavioral family therapy, support groups, 24-hour support, communication training, stress management, role play, homework, goal setting, development of social networks), measured outcomes, study design (e.g., setting, treatment duration, treatment frequency, follow-up duration, single family versus multiple family format, family members only versus family members plus patient), and demographics of the study population (e.g., age, illness duration, symptom severity at baseline). Most studies had small sample sizes and most had some risk of bias due to lack of reporting of randomization procedures or outcome assessment blinding. Studies conducted in China were excluded because of concerns about their applicability to United States populations.

In the AHRQ review (McDonagh et al. 2017), family interventions resulted in significantly lower relapse rates than usual care when measured at 0 to 6 months (three RCTs, N=244; 23% vs. 37%; RR 0.62, 95% CI 0.41 to 0.92; low SOE), 7-12 months (19 RCTs, N=1,118; 30% vs. 44%; RR 0.67, 95% CI 0.54 to 0.83; moderate SoE), 13-24 months (nine RCTs, N=517; 49% vs. 61%; RR 0.75, 95% CI 0.58 to 0.99; low SOE), and 5 years post-treatment (two RCTs, N=140; 78% vs. 94%; RR 0.82, 95% CI 0.72 to 0.94; low SOE) but not at 25 to 36 months. The strongest evidence for effects of family interventions on relapse occurred in studies that included at least 10 treatment sessions over 7 to 12 months.

Improvements in core illness symptoms (four RCTs, N=223; SMD -0.46, 95% CI -0.73 to -0.20; low SOE) and negative symptoms (three trials, N=163; SMD -0.38, 95% CI -0.69 to -0.07; low SOE) were also found with family intervention compared with usual care. Unemployment (four trials, N=230; 75% vs. 66% after 6-12 months of follow-up; RR 1.09, 95% CI 0.91 to 1.29; \(I^2=0\%\); low SOE), independent living (three RCTs, N=164; 57% vs. 63% at one year; RR 0.83, 95% CI 0.66 to 1.03; low SOE), or reduction in self-harm (six trials, N=314; 4% vs. 6%; RR 0.85, 95% CI 0.24 to 3.02; \(I^2=23\%\); low SOE) were not found to be different between family intervention and usual care groups (low SOE). For social functioning, quality of life, family burden, and non-suicide mortality, there was insufficient evidence to draw any conclusions from the available studies.

Rates of treatment discontinuation varied with time in the study, but family interventions either did not differ from usual care or had fewer treatment dropouts than usual care (McDonagh et al. 2017; low SOE).

**Statement 23**

APA suggests (2C) that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*

This guideline statement is based on three fair quality RCTs (total N=384; Bartels et al. 2014; Mueser et al. 2010; Valencia et al. 2007; Valencia et al. 2013) as described in the AHRQ review (McDonagh et al. 2017).

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* 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.
The strength of research evidence for this statement is rated as low based on the low SOE found for outcomes in the AHRQ review with social skills training.

In the trials of social skills training that were included in the AHRQ review (McDonagh et al. 2017), sessions were held weekly for 24 to 52 weeks and included specific, progressive intervention modules on topics such as management of symptoms and medication, improving social and family relationships, and increasing functional skills such as money management. Goals of social skills training included enhanced psychosocial function and reductions in relapse and need for hospitalization. Demographic parameters, diagnoses of participants, and outcome measures varied among the trials.

Social function was noted to be significantly improved with social skills training as compared to usual care (SMD on GAF at six months 1.60, 95% CI 1.19 to 2.02; SMD on GAF at one year 2.02, 95% CI 1.53 to 2.52; SMD on Multnomah Community Ability Scale at two years 0.65, 95% CI 0.36 to 0.95; low SOE), but it was not clear whether gains were maintained after treatment discontinuation. Core illness symptoms, as measured by the PANSS, also showed more improvement with social skills training as compared to usual care (SMD at 6 months -1.50, 95% CI -1.92 to -1.09; SMD at 2 years -0.81, 95% CI -1.22 to -0.40; low SOE). Negative symptoms also improved with social skills training as compared to usual care (SMD at 6 months -1.30, 95% CI -1.70 to -0.90; SMD at one year -0.82, 95% CI -1.23 to -1.40; SMD at two years -0.45, 95% CI -0.74 to -0.15; low SOE) and in one study gains were maintained one year after treatment had ended. It was unclear whether relapse rates were affected by social skills training because of a small number of studies, small sample sizes, and small numbers of individuals who experienced relapse. In terms of treatment discontinuation, individuals who received social skills training did not differ from those in the usual care group (RR 1.10 at one year, 95% CI 0.92 to 1.31; RR 1.01 at two years, 95% CI 0.88 to 1.16; low SOE) with high rates of treatment retention in both groups.
Appendix D. Strength of Evidence

The Strength of Evidence tables in this appendix are adapted from the AHRQ review (McDonagh et al. 2017) in which key outcomes are prioritized in terms of clinical and patient-centered outcomes. The prioritized outcomes are listed below, per intervention area. For more details, see Strength of the Body of Evidence and Appendix H References in the ARHQ review.

Pharmacological interventions:

- Functional outcomes (e.g., social, occupational)
- Health-related quality of life (including physical)
- Rates of response and/or remission
- Mortality (all-cause and/or specific)
- Reductions in self-harm, suicide, and suicide attempts
- Improvements in core illness symptoms scale score changes
- Overall/any adverse events (rate or proportion)
- Withdrawal due to adverse events

Psychosocial and other nonpharmacological interventions:

- Functional (e.g., social, occupational)
- Health-related quality of life
- Reductions in self-harm, suicide, and suicide attempts
- Rates of response and/or remission
- Improvements in core illness symptoms scale score changes
- Treatment discontinuation (typically reported as the number of patients lost to follow-up or leaving study early)
- Rates of relapse
- Outcomes reported as adverse events related to the intervention
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
<th>Strength of Evidence (High, Moderate, Low, Insufficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Functioning</td>
<td>Olanzapine, risperidone, quetiapine immediate-release</td>
<td>1 SR (2 RCTs; N =343, 1 observational study; N=9,028)</td>
<td>Moderate</td>
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<td></td>
<td></td>
<td></td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive:</td>
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<td>Observational</td>
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<td></td>
<td></td>
<td>evidence: Moderate</td>
<td>evidence: Unknown</td>
<td>evidence: Precise</td>
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<td>RCT 1: no significant differences on RFS or the SAS-SMI</td>
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<td>RCT 2: change on SFS greater with olanzapine (+7.75) than risperidone (-0.92, p=0.0028)</td>
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<td></td>
<td>Socially active: OR 1.27 (1.05 to 1.54); olanzapine 84.6% vs. risperidone 82.4%</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence</td>
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<tr>
<td>Social Functioning</td>
<td>Paliperidone monthly LAI vs. risperidone biweekly LAI</td>
<td>1 SR (2 RCTs; N=452)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No statistically significant differences in PSP scale</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>Paliperidone extended release vs. olanzapine</td>
<td>1 Meta-analysis of selected studies</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>No significant difference in PSP scale: mean change 7.8 to 12.2 in paliperidone dose groups vs. 8.7 in olanzapine group</td>
<td>Insufficient</td>
<td></td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td>Social Functioning</td>
<td>Risperidone LAI vs. quetiapine immediate release</td>
<td>1 RCT; N=666</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td></td>
<td>Risperidone LAI resulted in greater improvements in SOFA at 6 months (differences in change 6.1 vs. 2.7, p=0.02), 12 months (9.5 vs. 6.1, p=0.009), and endpoint (6.6 vs. 1.1, p&lt;0.0001).</td>
<td>Low</td>
</tr>
<tr>
<td>Employment Outcomes</td>
<td>Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)</td>
<td>1 SR (2 RCTs, 3 observational studies; N=1,379)</td>
<td>Low</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>No significant differences in rates of employment (mean 18% in CATIE Phase I)</td>
<td>Low</td>
</tr>
<tr>
<td>Function: Employment</td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (1 RCT; N=100)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Inconclusive: Proportion of patients with economic independence: RR 0.94 (0.68 to 1.29)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td>Function: Employment</td>
<td>Perphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=597)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Insufficient</td>
<td>Inconclusive: Proportion with paid employment: RR 1.29 (0.70 to 2.38)</td>
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<tr>
<td>Function: Employment</td>
<td>Perphenazine vs. quetiapine</td>
<td>1 SR (1 RCT; N=598)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Insufficient</td>
<td>Inconclusive: Proportion with paid employment: RR 1.75 (0.90 to 3.43)</td>
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<tr>
<td>Function: Employment</td>
<td>Perphenazine vs. risperidone</td>
<td>1 SR (1 RCT; N=602)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Insufficient</td>
<td>Inconclusive: Proportion with paid employment: RR 1.38 (0.74 to 2.57)</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td>Function: Employment</td>
<td>Perphenazine vs. ziprasidone</td>
<td>1 SR (1 RCT; N=446)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Proportion with paid employment: RR 1.22 (0.60 to 2.51)</td>
<td>Insufficient</td>
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<tr>
<td>Occupation and Residential Status</td>
<td>Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)</td>
<td>1 SR (21 RCT; N=771)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: 75.5% and 75.3% had stable status, 3.8% and 3.1% had improved status (NS)</td>
<td>Insufficient</td>
<td></td>
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<tr>
<td>Global Functioning (GAF)</td>
<td>Olanzapine vs. Risperidone</td>
<td>1 SR (4 cohort studies; N=3,211)</td>
<td>High</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: Pooled WMD 0.61 (-1.78 to 2.99), I²=43%</td>
<td>Low</td>
<td></td>
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<tr>
<td>Global Functioning (GAF)</td>
<td>Olanzapine vs. Quetiapine</td>
<td>1 SR (2 RCTs; N=363)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Pooled WMD 1.14 (-4.75 to 7.02); Q=3.99, df=1, p=0.045</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td><strong>Function: General</strong></td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (1 RCT; N=208)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: GAF effect estimate: -4.00 (-13.70 to 5.70)</td>
<td>Insufficient</td>
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<tr>
<td><strong>Function: Encounters with Legal System</strong></td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (1 RCT; N=31)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Encounters with legal system: RR 3.20 (0.76 to 13.46)</td>
<td>Insufficient</td>
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<tr>
<td><strong>Quality of Life</strong></td>
<td>Olanzapine vs. risperidone</td>
<td>1 SR (2 RCTs; N=492)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>QLS Change: 7 months 13.4 vs. 8.8 (p&gt;0.074); 12 months 0.19 vs. 0.26 (p=0.53)</td>
<td>Moderate</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td>Quality of Life Olanzapine vs. ziprasidone</td>
<td>1 SR (2 RCTs; N=740)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>QLS Change: 6-7 months 61.3 vs. 58.9 (p=0.36 using mixed-effect modeling); 12 months 0.19 vs. 0.26 (p NR)</td>
<td>Moderate</td>
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<tr>
<td>Quality of Life Olanzapine vs. quetiapine immediate release</td>
<td>1 SR (1 RCT; N=227)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>QLS Change: 12 months 0.19 vs. 0.09 (p&gt;0.05)</td>
<td>Low</td>
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<tr>
<td>Quality of Life Olanzapine vs. asenapine</td>
<td>1 SR (1 RCT; N=464)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>QLS Change: 12 months 11.7 vs. 11.8 and 11.1 vs. 7.1 (multicountry study reported by hemisphere; p=NS)</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life Olanzapine vs. clozapine</td>
<td>1 SR (1 RCT; N=114)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>SWN scale: at 26 weeks, olanzapine found non-inferior to clozapine; difference 3.2 (4.2 to 10.5)</td>
<td>Insufficient</td>
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<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td>Quality of Life</td>
<td>Risperidone vs. ziprasidone</td>
<td>1 SR (N=154)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>QLS Change: 12 months 0.19 vs. 0.26 (p&gt;0.05)</td>
<td>Low</td>
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<tr>
<td>Quality of Life</td>
<td>Risperidone vs. quetiapine</td>
<td>1 SR (1 RCT; N=189)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>QLS Change: 12 months 0.26 vs. 0.26 (p&gt;0.05)</td>
<td>Low</td>
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<tr>
<td>Quality of Life</td>
<td>Quetiapine extended release vs. risperidone</td>
<td>1 RCT; N=798</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>SWN short form 20% response rate at 6 months: 65% vs. 68%; adjusted difference -5.7% (-15.1 to 3.7) but not meeting non-inferiority criteria</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life</td>
<td>Aripiprazole oral vs. aripiprazole LAI (monthly)</td>
<td>1 RCT; N=724</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>SF-36 12 months: mean changes in mental component 0.82 vs. 0.38; difference 0.44 (-1.24 to 2.12) and physical component 0.23 vs. -0.27; difference 0.50 (-1.11 to 2.11)</td>
<td>Low</td>
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<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
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<tr>
<td>Quality of Life</td>
<td>Aripiprazole LAI vs. paliperidone palmitate LAI (monthly)</td>
<td>1 RCT; N=295</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>QLS Change: 28 weeks 7.47 vs. 2.80; least squares mean difference 4.67 (0.32 to 9.02). Meets non-inferiority criteria; does not meet minimally clinical important difference</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life</td>
<td>Risperidone LAI vs. quetiapine</td>
<td>1 RCT; N=666</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>SF-12 physical and mental component scores and QLS-Revision 4 scores improved from baseline in both groups but were not significantly different at endpoint, 24 months (SF-12 physical, p=0.09; SF-12 mental and QLS-R4, p=NR).</td>
<td>Low</td>
<td></td>
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<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Quality of Life</td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (5 RCTs; N=816)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Inconclusive: Effect sizes ranged from -3.62 to 0 using different measures; CIs were not significant</td>
<td>Moderate</td>
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<tr>
<td>Quality of Life</td>
<td>Haloperidol vs. quetiapine</td>
<td>1 SR (1 RCT; N=207)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Effect estimate 0.00 (-1.38 to 1.38)</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life</td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (2 RCTs; N=352)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Effect estimates ranged from -0.10 to 0.10; CIs were not significant</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence</td>
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<tr>
<td>Quality of Life</td>
<td>Haloperidol vs. ziprasidone</td>
<td>1 SR (2 RCTs; N=784)</td>
<td>High</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Studies favored ziprasidone in quality of life measures. One trial found effect favoring ziprasidone based on QLS: effect estimate -12.12 (-22.06 to -2.17); there was no difference in another trial in MANS: effect estimate -0.10 (-1.48 to 1.28)</td>
<td>Low</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Perphenazine vs. aripiprazole</td>
<td>1 SR (1 RCT; N=300)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Inconclusive: Proportion with 20% improvement: RR 4.74 (2.58 to 8.69)</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life</td>
<td>Perphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=597)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td></td>
<td>No difference: Effect estimate 0.00 (-0.16 to 0.16)</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Quality of Life</td>
<td>Perphenazine vs. quetiapine</td>
<td>1 SR (1 RCT; N=598)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: Effect estimate 0.10 (-0.07 to 0.27)</td>
<td>Low</td>
<td></td>
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<tr>
<td>Quality of Life</td>
<td>Perphenazine vs. risperidone</td>
<td>1 SR (1 RCT; N=602)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: Effect estimate -0.07 (-0.24 to 0.10)</td>
<td>Low</td>
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<tr>
<td>Quality of Life</td>
<td>Perphenazine vs. ziprasidone</td>
<td>1 SR (1 RCT; N=446)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: Effect estimate -0.07 (-0.27 to 0.13)</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Response</td>
<td>Network meta-analysis of olanzapine, risperidone, quetiapine IR, aripiprazole, clozapine, ziprasidone, asenapine, paliperidone, aripiprazole LAI monthly, caripipramine, brexipiprazole, lurasidone</td>
<td>46 RCTs; N=12,536</td>
<td>Moderate Consistent Indirect Precise</td>
<td>There were 2 statistically significant differences between the drugs; both olanzapine (OR 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) were significantly more likely to result in response than quetiapine IR.</td>
<td>Low</td>
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<tr>
<td>Response</td>
<td>Fluphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=60)</td>
<td>Moderate Unknown Direct Imprecise</td>
<td>Inconclusive: RR 0.74 (0.51 to 1.07)</td>
<td>Insufficient</td>
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<tr>
<td>Response</td>
<td>Fluphenazine vs. quetiapine</td>
<td>1 SR (1 RCT; N=25)</td>
<td>Moderate Unknown Direct Imprecise</td>
<td>Inconclusive: RR 0.62 (0.12 to 3.07)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
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<tr>
<td>Response</td>
<td>Fluphenazine vs. risperidone</td>
<td>1 SR (1 RCT; N=26)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.67 (0.13 to 3.35)</td>
<td>Insufficient</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. aripiprazole</td>
<td>1 SR (5 RCTs; N=2,185)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: RR 1.01 (0.76 to 1.34), I²=83%</td>
<td>Low</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. asenapine</td>
<td>1 SR (1 RCT; N=335)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.82 (0.64 to 1.04)</td>
<td>Insufficient</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. clozapine</td>
<td>1 SR (2 RCTs; N=144)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.64 (0.28 to 1.47), I²=72%</td>
<td>Insufficient</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (14 RCTs; N=4,099)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Favors olanzapine: RR 0.86 (0.78 to 0.96), I²=55%</td>
<td>Low</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. quetiapine</td>
<td>1 SR (6 RCTs; N=1,421)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: RR 0.99 (0.76 to 1.30), I²=77%</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
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<td>Directness</td>
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<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (16 RCTs; N=3,452)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: RR 0.94 (CI 0.87 to 1.02), I²=29%</td>
<td>Moderate</td>
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<tr>
<td>Response</td>
<td>Haloperidol vs. ziprasidone</td>
<td>1 SR (6 RCTs; N=1,283)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.98 (0.74 to 1.30), I²=80%</td>
<td>Low</td>
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<tr>
<td>Response</td>
<td>Perphenazine vs. aripiprazole</td>
<td>1 SR (1 RCT; N=300)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.95 (0.64 to 1.40)</td>
<td>Insufficient</td>
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<tr>
<td>Remission</td>
<td>Haloperidol vs. clozapine</td>
<td>1 SR (1 RCT; N=71)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.16 (0.02 to 1.20)</td>
<td>Insufficient</td>
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<tr>
<td>Remission</td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (3 RCTs; N=582)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Favors olanzapine: RR 0.65 (0.45 to 0.94), I²=54%</td>
<td>Low</td>
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<tr>
<td>Remission</td>
<td>Haloperidol vs. quetiapine</td>
<td>1 SR (1 RCT; N=207)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.72 (0.41 to 1.25)</td>
<td>Insufficient</td>
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<td>Outcome</td>
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<td>Number of Studies</td>
<td>Number of Subjects</td>
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<td>Directness</td>
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<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Remission</td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (2 RCTs; N=179)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Inconclusive: RR 0.84 (0.56 to 1.24), I²=0%</td>
<td>Low</td>
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<tr>
<td>Remission</td>
<td>Haloperidol vs. ziprasidone</td>
<td>1 SR (3 RCTs; N=1,085)</td>
<td>High</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td></td>
<td>No difference: RR 0.89 (0.71 to 1.12), I²=12%</td>
<td>Low</td>
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<tr>
<td>Mortality (All-Cause)</td>
<td>Olanzapine vs. risperidone vs. quetiapine</td>
<td>1 SR (1 retrospective cohort study; N=48,595)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td></td>
<td>No difference in all-cause mortality between risperidone and olanzapine (HR 1.09, 95% CI 0.79 to 1.49) or quetiapine (HR 0.75, 95% CI 0.53 to 1.07).</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
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<tr>
<td>Mortality (All-Cause)</td>
<td>Clozapine, risperidone, olanzapine and quetiapine vs. no treatment</td>
<td>1 SR (1 retrospective cohort study; N=6,987)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72), and risperidone and olanzapine were not statistically significantly different from control.</td>
<td>Insufficient</td>
<td></td>
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<tr>
<td>Mortality (All-Cause)</td>
<td>Asenapine vs. olanzapine</td>
<td>2 RCTs; N=2,174 (1 RCT reported 2 RCT studies)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RCT 1: 0.41% vs. 0.42% RCT 2: 0% vs. 0.77% RCT 3: 0.32% RR 2.49 (0.54 to 11.5)</td>
<td>Low</td>
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<tr>
<td>Mortality (All-Cause)</td>
<td>Paliperidone palmitate LAI (monthly) vs. risperidone LAI</td>
<td>2 RCTs; N=752</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RCT 1: 0.79% vs. 0.27% RCT 2: 0% vs. 0.45% RR 1.26 (0.21 to 7.49)</td>
<td>Low</td>
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<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
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<tr>
<td>Mortality (All-Cause)</td>
<td>Quetiapine vs. risperidone</td>
<td>2 RCTs; N=1,057</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RCT 1: 1.17% vs. 0.40% RCT 2: 0.72% vs. 0% RR 3.24 (0.72 to 14.6)</td>
<td>Low</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>Olanzapine vs. risperidone vs. quetiapine</td>
<td>1 SR (2 retrospective cohort study; N=55,582)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No significant differences between the drugs: HRs 0.99 (0.37 to 2.67) and 0.76 (0.25 to 2.28), respectively</td>
<td>Low</td>
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</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>Clozapine vs. risperidone</td>
<td>1 SR (2 retrospective cohort studies; N=1,686)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: No significant differences between drugs: 4.8% vs. 2.5%; RR 1.39 (0.61 to 2.53)</td>
<td>Insufficient</td>
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</tr>
<tr>
<td>Self-Harm: Suicidal Behavior, Suicide</td>
<td>Clozapine vs. olanzapine in high-risk patients</td>
<td>1 SR (1 RCT; N=980)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suicidal behavior: HR 0.76 (0.58 to 0.97)</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
<td>Strength of Evidence (High, Moderate, Low, Insufficient)</td>
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<tr>
<td><strong>Self-Harm: Suicidal Behavior, Suicide</strong></td>
<td>Clozapine vs. olanzapine in high-risk patients</td>
<td>1 SR (1 RCT; N=980)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Worsening on CGI-Suicide Severity: HR 0.78 (0.61 to 0.99)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Self-Harm: Suicidal Behavior, Suicide</strong></td>
<td>Clozapine vs. olanzapine in high-risk patients</td>
<td>1 SR (1 RCT; N=980)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suicide deaths: No significant differences (5 clozapine, 3 olanzapine)</td>
<td>Low</td>
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</tr>
<tr>
<td><strong>Self-Harm: Suicidal Behavior, Suicide</strong></td>
<td>Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole</td>
<td>1 SR (2 retrospective cohorts; N=16,584)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Death by suicide lower with clozapine: OR 0.29 (0.14 to 0.63) compared with no treatment at 6 months and lower with clozapine (1.1%) than baseline (2.2%) or other drugs (range 2.1% to 3.7%) at 1 year</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
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<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Self-Harm: Suicidal Behavior, Suicide</td>
<td>Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole</td>
<td>1 SR (1 prospective cohort; N=10,204)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Suicide attempts (6 months): No statistically significant difference between drugs</td>
<td>Insufficient</td>
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<tr>
<td>Self-Harm: Suicidal Behavior, Suicide</td>
<td>Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole</td>
<td>1 SR (1 prospective cohort; N=20,489)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Inconclusive: Suicide attempts or death by suicide: aripiprazole vs. all others combined HR 0.69 (0.42 to 1.14)</td>
<td>Insufficient</td>
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<tr>
<td>Reduction in Self Harm</td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (1 RCT; N=182)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: Attempted suicide: RR 3.13 (0.13 to 76)</td>
<td>Insufficient</td>
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<td>Completed suicide: RR 3.13 (0.13 to 76)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
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<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Reduction in Self Harm</td>
<td>Perphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=597)</td>
<td></td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: Attempted suicide: RR 0.64 (0.06 to 7.06)</td>
<td>Insufficient</td>
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<td>Completed suicide: RR 3.86 (0.40 to 37)</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
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<td>Core Illness Symptoms</td>
<td>Oral SGAs (except caripipramine): meta-analysis of clozapine, amisulpride,</td>
<td>212 RCTs; N=43,049</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Precise</td>
<td>Clozapine had significantly better improvement than the other drugs except olanzapine: SMDs on PANSS or BPRS -0.32 to -0.55. Olanzapine and risperidone superior to the other drugs, except for each other and paliperidone: SMDs -0.13 to -0.26. Paliperidone superior to lurasidone and iloperidone: SMD -0.17. All drugs superior to placebo: SMDs -0.33 to -0.88.</td>
<td>Low</td>
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<tr>
<td></td>
<td>olanzapine, risperidone, paliperidone, zotepine, haloperidol, quetiapine,</td>
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<td>aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone, and iloperidone</td>
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<tr>
<td><strong>Core Illness Symptoms</strong></td>
<td>Treatment resistant patients: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone</td>
<td>Network meta-analysis (40 RCTs; N=5,172)</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Precise</td>
<td>The only significant difference was that the mean change in the PANSS was greater with olanzapine than quetiapine: SMD -0.29 (-0.56 to -0.13)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Core Illness Symptoms</strong></td>
<td>Brexpiprazole vs. aripiprazole</td>
<td>1 open label study; N=97</td>
<td></td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: PANSS: least square means difference -22.9 vs. -19.4 at 6 weeks from baseline; direct comparison not reported.</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Overall/Any Adverse Events</strong></td>
<td>Asenapine vs. olanzapine</td>
<td>5 RCTs (4 publications; N=2,189)</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Pooled RR 1.00 (0.96 to 1.05), I²=9%</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Overall/Any Adverse Events</strong></td>
<td>Quetiapine vs. risperidone</td>
<td>7 RCTs; N=3,254</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Pooled RR 1.04 (0.97 to 1.12), I²=56%</td>
<td>Moderate</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
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<tr>
<td>Overall/Any Adverse Events</td>
<td>Clozapine vs. olanzapine</td>
<td>2 RCTs; N=182</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Pooled RR 1.15 (1.00 to 1.33), I²=0%</td>
<td>Low</td>
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<tr>
<td>Overall/Any Adverse Events</td>
<td>Risperidone vs. olanzapine</td>
<td>5 RCTs; N=873</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Pooled RR 1.02 (0.81 to 1.29), I²=77%</td>
<td>Low</td>
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</tr>
<tr>
<td>Overall/Any Adverse Events</td>
<td>Olanzapine vs. ziprasidone</td>
<td>5 RCTs; N=1,097 (6 weeks to 6 months durations)</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Pooled RR 1.00 (0.86 to 1.16), I²=80%</td>
<td>Low</td>
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<tr>
<td>Overall/Any Adverse Events</td>
<td>Olanzapine vs. quetiapine</td>
<td>3 RCTs; N=448</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Pooled RR 0.90 (0.74 to 1.11), I²=30%</td>
<td>Low</td>
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<tr>
<td>Overall/Any Adverse Events</td>
<td>Quetiapine extended release vs. quetiapine immediate release and risperidone; risperidone vs. clozapine and aripiprazole; olanzapine vs. paliperidone; risperidone LAI vs. paliperidone and paliperidone palmitate monthly LAI; and aripiprazole vs. aripiprazole monthly LAI. Additionally, there were six trials comparing asenapine and olanzapine</td>
<td>1 SR (28 RCTs; N=7,810)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No statistically significant differences were found in each comparison.</td>
<td>Low</td>
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<tr>
<td>Overall/Any Adverse Events</td>
<td>Oral-aripiprazole vs. brexipiprazole, olanzapine, paliperidone, and risperidone LAI; ziprasidone vs. clozapine, risperidone, iloperidone and lurasidone; risperidone vs. asenapine, carpipramine and risperidone LAI; clozapine vs. quetiapine, quetiapine vs. risperidone LAI; olanzapine vs. olanzapine LAI and lurasidone; aripiprazole monthly LAI vs. paliperidone; and paliperidone palmitate monthly LAI vs. 3-monthly LAI.</td>
<td>1 SR (31 RCTs; N=6,700)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No statistically significant differences were found in single studies of each comparison.</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
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<tr>
<td>Overall Adverse Events</td>
<td>Haloperidol vs. aripiprazole</td>
<td>1 SR (3 RCTs; N=1,713)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.11 (1.06 to 1.17), I²=0%; less with aripiprazole</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (8 RCTs; N=1,313)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.20 (1.01 to 1.42), I²=84%; less with risperidone</td>
<td>Moderate</td>
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<td></td>
<td>Haloperidol vs. ziprasidone</td>
<td>1 SR (6 RCTs; N=1,448)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.13 (1.03 to 1.23), I²=31%; less with ziprasidone</td>
<td>Moderate</td>
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</table>
### Discontinuation Due to Adverse Events

|                  | Network meta-analysis of aripiprazole, aripiprazole monthly LAI, asenapine, brexipiprazole, cariprazine, clozapine, iloperidone, lurasidone10, olanzapine, olanzapine LAI, paliperidone 3-month LAI, paliperidone, paliperidone Monthly LAI, quetiapine ER, quetiapine IR, risperidone, risperidone LAI, ziprasidone | 89 RCTs (N = 29,678) | Moderate | Consistent | Indirect | Precise | Risperidone LAI had statistically significantly lower risk of withdrawals due to adverse events than asenapine (OR 0.50, 95% CI 0.23 to 0.97); clozapine (OR 0.26, 95% CI 0.10 to 0.67); lurasidone (OR 0.38, 95% CI 0.17 to 0.79); paliperidone (OR 0.43, 95% CI 0.17 to 0.98); paliperidone LAI monthly (OR 0.51, 95% CI 0.26 to 0.98); quetiapine ER (OR 0.42, 95% CI 0.21 to 0.78); risperidone (OR 0.48, 95% CI 0.23 to 0.92); and ziprasidone (OR 0.39, 95% CI 0.18 to 0.76). Olanzapine had lower risk than clozapine (OR 0.40, 95% CI 0.21 to 0.79); lurasidone (OR 0.58, 95% CI 0.36 to 0.98); quetiapine IR (OR 0.64, 95% CI 0.45 to 0.93); risperidone (OR 0.74, 95% CI 0.55 to 0.98); and | Low |

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<th>Outcome</th>
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<th>Number of Studies</th>
<th>Study Limitations</th>
<th>Consistency</th>
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<td>ziprasidone (OR 0.59, 95% CI 0.43 to 0.84).</td>
<td>Insufficient</td>
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<td>Aripiprazole had lower risk than ziprasidone (OR 0.65, 95% CI 0.44 to 0.95) and iloperidone had lower risk than clozapine (OR 0.35, 95% CI 0.13 to 0.91).</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Fluphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=60)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.74 (0.51 to 1.07)</td>
<td>Insufficient</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Fluphenazine vs. quetiapine</td>
<td>1 SR (1 RCT; N=25)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.19 (0.01 to 3.52)</td>
<td>Insufficient</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. asenapine</td>
<td>1 SR (1 RCT; N=335)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.53 (0.74 to 3.16)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
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<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. aripiprazole</td>
<td>1 SR (7 RCTs)</td>
<td>3,232</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.25 (1.07 to 1.47), I²=0%</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. clozapine</td>
<td>1 SR (5 RCTs)</td>
<td>719</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.00 (0.66 to 1.50), I²=0%</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. olanzapine</td>
<td>1 SR (21 RCTs)</td>
<td>5,708</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.89 (1.57 to 2.27), I²=0%</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. quetiapine</td>
<td>1 SR (8 RCTs)</td>
<td>1,759</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.97 (0.96 to 4.01), I²=62%</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. risperidone</td>
<td>1 SR (23 RCTs)</td>
<td>4,581</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.32 (1.09 to 1.60), I²=0%</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Haloperidol vs. ziprasidone</td>
<td>1 SR (6 RCTs) plus 1 RCT; N=1,597</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>RR 1.68 (1.26 to 2.23), I²=0%</td>
<td>Moderate</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Perphenazine vs. aripiprazole</td>
<td>1 SR (1 RCT; N=300)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.53 (0.27 to 1.05)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Perphenazine vs. olanzapine</td>
<td>1 SR (1 RCT; N=597)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.83 (0.58 to 1.19)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Perphenazine vs. quetiapine</td>
<td>1 SR (1 RCT; N=598)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.05 (0.72 to 1.55)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Perphenazine vs. risperidone</td>
<td>1 SR (1 RCT; N=602)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.54 (1.00 to 2.36)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
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<tr>
<td>Withdrawal Due to Adverse Events</td>
<td>Perphenazine vs. ziprasidone</td>
<td>1 SR (1 RCT; N=446)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.01 (0.65 to 1.58)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

BPRS=Brief Psychiatric Rating Scale, CATIE=clinical Antipsychotic Trials of Intervention Effectiveness, CGI-S=Clinical Global Impression-Severity, CI=confidence interval, ER=efficacy ratio, GAF=Global Assessment of Functioning, HR=hazard ratio, LAI=long acting injectable, MANSAL=Manchester Short Assessment of Quality of Life, NR=normal range, NS=not significant, NSD=no significant difference, OR=odds ratio, PANSS=Positive and Negative Syndrome Scale, PSP=Personal and Social Performance, Q=Cochran’s Q test, QLS=Quality of Life Scale, RCT=randomized controlled trial, RFS=Role Functioning Scale, RR=relative risk, SAS=Social Adjustment Scale, SAS-SMI=Social Adjustment Scale-Severely Mentally Ill version SF=short form, SFS=Social Functioning Scale, SGA=second-generation antipsychotic, SMD=standard mean difference, SOFA=Social and Occupational Functioning Assessment, SQLS=Schizophrenia Quality of Life Scale, SR=systematic review, SWN=Subjective Well-being under Neuroleptic Treatment, WMD=weighted mean difference.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Strength of Evidence Domain: Study Limitations</th>
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</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (3 RCTs) plus 1 RCT; N=118</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No difference in social function compared with usual care. Social function: mean difference 0.03 (-0.28 to 0.34)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Trouble with Police</strong></td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (4 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No differences in arrests (2 trials; OR 1.17, 95% CI 0.60 to 2.29), imprisonment (4 trials; OR 1.19, 95% CI 0.70 to 2.01), or police contacts (2 trials; OR 0.76, 95% CI 0.32 to 1.79)</td>
<td>Low</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
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<td>Number of Subjects</td>
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<tr>
<td>Housing and Independent Living</td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (3 RCTs) plus 1 RCT; N=118</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Less likely to be not living independently (4 trials; OR 0.52, 95% CI 0.35 to 0.79) and to be homeless (4 trials; OR 0.20, 95% CI 0.09 to 0.47). Less likely to be homeless (4 trials, OR 0.24, 95% CI 0.12 to 0.48).</td>
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<tr>
<td>Employment</td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (3 RCTs)</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Less likely to be unemployed (OR 0.46, 95% CI 0.21 to 0.99)</td>
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<td>Outcome</td>
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<tr>
<td>Quality of Life</td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (1 RCT; N=125) plus 1 RCT; N=118</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Quality of life was slightly better with assertive community treatment (mean difference -0.52, 95% CI -0.99 to -0.05) in one trial, but no differences found in the other trial.</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Overall Symptoms</td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (3 RCTs) plus 1 RCT; N=118</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No differences were found in 4 trials (mean difference -0.14, 95% CI -0.36 to 0.08).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
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<td>Strength of Evidence Domain: Study Limitations</td>
<td>Strength of Evidence Domain: Consistency</td>
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<tr>
<td>Treatment Maintenance (Loss to follow-up)</td>
<td>Assertive community treatment vs. usual care</td>
<td>1 SR (10 RCTs) plus 1 RCT; N=118</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Significantly less loss to follow-up with assertive community treatment (OR 0.51, 95% CI 0.40 to 0.65) based on 10 trials in SR; and significantly fewer patients “out-of-care” in the other trial (OR 0.10, 95% CI 0.03 to 0.33)</td>
<td>Moderate</td>
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CI=confidence interval, OR=odds ratio, RCT=randomized controlled trial, SR=systematic review
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<tr>
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<th>Number of Subjects</th>
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<th>Strength of Evidence Domain: Directness</th>
<th>Strength of Evidence Domain: Precision</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Function: Global Function – Short term (≤6 months since CBT initiation)</td>
<td>CBT vs. usual care</td>
<td>1 SR (3 RCTs) plus 5 RCTs; N=701</td>
<td>Moderate Consistent Direct Precise</td>
<td>GAF (6 RCTs): mean difference 5.49 (1.85 to 9.14), $I^2=75%$; excluding one outlier: 6.62 (4.68 to 8.56), $I^2=0%$ SOFAS (2 RCTs): mean difference 9.11 (6.31 to 11.91) Proportion with normal function (1 RCT): RR 2.21 (1.25 to 3.93)</td>
<td>Moderate</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
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<tr>
<td>Function: Global Function – Medium term (&gt;6 months to 1 year since CBT initiation)</td>
<td>CBT vs. usual care</td>
<td>3 RCTs; N=465</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: GAF: one trial with 6 months posttreatment follow-up found no difference. Another trial found effect favoring CBT. SOFAS, SFS: No difference between groups</td>
<td>Insufficient</td>
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<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Number of Subjects</th>
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<th>Strength of Evidence Domain: Consistency</th>
<th>Strength of Evidence Domain: Directness</th>
<th>Strength of Evidence Domain: Precision</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
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<tbody>
<tr>
<td><strong>Function: Global Function – Long term (&gt;1 year since CBT initiation)</strong></td>
<td>CBT vs. usual care</td>
<td>1 SR (4 RCTs) plus 4 RCTs; N=851</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: GAF: 1 SR found mean difference 4.20 (-0.63 to 9.03). One other RCT found positive effect of CBT. 3 RCTs found no difference in SOFAS, global function (scale not reported) and proportion of patients with normal function.</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Function: Basic Living Skills</strong></td>
<td>CBT vs. usual care</td>
<td>1 RCT; N=76</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No difference between groups.</td>
<td>Insufficient</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
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<td>Number of Studies</td>
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<tr>
<td><strong>Function:</strong> Employment Outcomes</td>
<td>CBT vs. usual care</td>
<td>2 RCTs; N=522</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: One RCT of vocational-focused CBT favored CBT for hours worked and WBI score; another trial found no difference in proportion of patients with occupational recovery</td>
<td>Insufficient</td>
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<tr>
<td><strong>Quality of Life</strong></td>
<td>CBT vs. usual care</td>
<td>12-24 weeks follow-up; 2 RCTs; N=216</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>CBT led to improved quality of life 0 and 16 weeks after cessation of treatment based on CHOICE, WEMWEBS, and WHOQOL-BREF scales.</td>
<td>Low</td>
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</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>CBT vs. usual care</td>
<td>18 to 24 months follow-up; 2 RCTs; N=489</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>CBT not different from usual care based on WHOQOL and EROQOL scales</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
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<tr>
<td>Suicide and Suicidality</td>
<td>CBT vs. usual care</td>
<td>2 RCTs; N=307</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.68 (0.12 to 3.93) and RR 0.53 (0.12 to 2.79)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Core Illness Symptoms</td>
<td>CBT vs. usual care</td>
<td>1 SR (34 RCTs; N=2,989)</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>SMD -0.33 (0.47 to -0.19); subgroup with outcome assessment blinding SMD -0.15 (-0.27 to -0.03)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>CBT vs. usual care</td>
<td>2 SRs (34 RCTs; N=3,393)</td>
<td></td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>SMD -0.13 (-0.25 to -0.01), I²=48% (in this review a negative estimate favors CBT); and SMD 0.09 (-0.03 to 0.21), I²=63% (in this review, a positive estimate favors CBT)</td>
<td>Low</td>
</tr>
<tr>
<td>Ability to Maintain Treatment</td>
<td>CBT vs. usual care</td>
<td>13 RCTs; N=1,847</td>
<td></td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No difference: RR 1.03 (0.96 to 1.10), I²=64%</td>
<td>Low</td>
</tr>
<tr>
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<tr>
<td>Relapse</td>
<td>CBT vs. usual care</td>
<td>6 RCTs; N=1,090</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.80 (0.51 to 1.25), I²=77%</td>
<td>Sub-analysis limited to relapse defined as “hospitalization” (3 RCTs): 0.70 (0.54 to 0.91), I²=0%</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Harms</td>
<td>CBT vs. usual care</td>
<td>1 RCT; N=150</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>None of the adverse events were related to treatment: 2 vs. 4 suicide attempts; 1 vs. 1 serious violent incident</td>
<td>Insufficient</td>
<td></td>
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</tbody>
</table>

CBT=cognitive behavioral therapy, CI=confidence interval, CHOICE=CHoice of Outcome In Cbt for psychoses, EROQOL= European Quality of Life scale, GAF=Global Assessment of Functioning, OR=odds ratio, RCT=randomized controlled trial, RR=relative risk, SFS=Social Functioning Scale, SMD=standard mean difference, SOFAS=Social and Occupational Functioning Assessment Scale, SR=systematic review, WBI=Work Behavior Inventory, WEMWEBS=Warwick-Edinburgh Mental Well-being Scale, WHOQOL= World Health Organization Quality of Life
<table>
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<tr>
<td>Function</td>
<td>Cognitive remediation vs. usual care</td>
<td>1 SR (19 RCTs) plus 3 RCTs; N=1,323</td>
<td>1,323</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>In studies comparing with usual care, cognitive remediation resulted in a small positive effect on function that was not consistently statistically significant: effect size 0.16 (-0.16 to 0.49); SMD 0.56 (0.34 to 0.88) and SMD 0.41 (-.10 to 0.91).</td>
<td>Low</td>
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<tr>
<td>Quality of life</td>
<td>Cognitive remediation vs. usual care</td>
<td>1 RCT; N=69</td>
<td>69</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Quality of life was only reported in one trial, with no difference between cognitive remediation and usual care.</td>
<td>Insufficient</td>
</tr>
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<tr>
<td>Overall symptoms</td>
<td>Cognitive remediation vs. usual care</td>
<td>2 RCTs; N=153</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Cognitive remediation improved total symptoms based on 2 trials: SMD -0.62 (-1.01 to -0.24). Four trials included in the Wykes review reported effect sizes ranging from 0.05 to 0.45 (95% CIs were not reported).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Cognitive remediation vs. usual care</td>
<td>1 SR (18 RCTs; N=781)</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Negative symptoms improved more in cognitive remediation groups: effect size -0.36 (-0.52 to -0.20); a negative effect size favors cognitive remediation.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ability to maintain treatment</td>
<td>Cognitive remediation vs. usual care</td>
<td>3 RCTs; N=302</td>
<td></td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>There was no difference in ability to maintain treatment in three RCTs of cognitive remediation</td>
<td>Low</td>
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### Family interventions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Strength of Evidence Domain: Study Limitations</th>
<th>Strength of Evidence Domain: Consistency</th>
<th>Strength of Evidence Domain: Directness</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function: Occupational (Unemployed) - 1 year</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (4 RCTs; N=230)</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 1.09 (0.92 to 1.29)</td>
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<tr>
<td>Function: Occupational (Unemployed) - 2 years</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=51)</td>
<td>Moderate Unknown Direct Imprecise</td>
<td>RR 1.33 (0.84 to 2.10)</td>
<td>Insufficient</td>
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<tr>
<td>Function: Occupational (Unemployed) - 3 years</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=99)</td>
<td>Moderate Unknown Direct Imprecise</td>
<td>RR 1.19 (0.92 to 1.55)</td>
<td>Insufficient</td>
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<tr>
<td>Function: Living situation (cannot live independently) - 1 year</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (3 RCTs; N=164)</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 0.83 (0.66 to 1.03)</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
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<td>Strength of Evidence Domain: Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Function: Living situation (cannot live independently) - 3 years</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=99)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>RR 0.82 (0.59 to 1.14)</td>
<td>Insufficient</td>
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<tr>
<td>Function: Living situation (cannot live independently, months in psychiatric facility) - 5 years</td>
<td>Family intervention vs. usual care</td>
<td>1 RCT; N=73</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>10.87 vs. 21.18 months, p=0.04</td>
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<tr>
<td>Social Functioning</td>
<td>Family intervention vs. usual care</td>
<td>1 RCT; N=69</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No between group differences</td>
<td>Insufficient</td>
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<tr>
<td>Quality of Life</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=50) plus one RCT not in SR; N=55</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Heinrichs scale: MD -5.05 (-15.44 to 5.34) EUROQOL: MD -7.38 (-22.07 to 7.31)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
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<td>Number of Subjects</td>
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<td>Strength of Evidence Domain: Consistency</td>
<td>Strength of Evidence Domain: Directness</td>
<td>Strength of Evidence Domain: Precision</td>
<td>Magnitude of Effect: Summary Effect Size (95% CI)</td>
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<tr>
<td>Depression</td>
<td>Family intervention vs. usual care</td>
<td>2 RCTs; N=124</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>RCT 1, 6 months: -1.0 (-12 to 22) vs. 0 (-15 to 17)</td>
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<td>RCT 1, 12 months: 3.0 (-15 to 17) vs. 0 (-14 to 17)</td>
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<td>RCT 2, 12 months: 3.35 (-2.64 to 9.34)</td>
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<td>RCT 2, 24 months: -0.11 (-6.91 to 6.68)</td>
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<tr>
<td>Anxiety</td>
<td>Family intervention vs. usual care</td>
<td>1 RCT; N=55</td>
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<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>12 months: -0.42 (-6.97 to 6.13)</td>
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<td>24 months: -2.36 (-9.13 to 4.40)</td>
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<td>Suicide</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (6 RCTs; N=314)</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>RR 0.85 (0.24 to 3.02)</td>
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<td>Core Illness Symptoms:</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (2 RCTs; N=223)</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>SMD -0.46 (-0.73 to -0.20)</td>
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<td>Strength of Evidence Domain: Directness</td>
<td>Strength of Evidence Domain: Precision</td>
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<tr>
<td>Negative Symptoms</td>
<td>Family intervention vs. usual care</td>
<td>3 RCTs; N=163</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>SMD -0.38 (-0.69 to -0.07)</td>
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<tr>
<td>Leaving the study early (3-6 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (6 RCTs; N=504)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>RR 0.86 (0.50 to 1.47)</td>
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<tr>
<td>Leaving the study early (7-12 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (9 RCTs; N=487) plus 4 RCTs; N=466</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>RR 0.77 (0.64 to 0.93)</td>
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<tr>
<td>Leaving the study early (13-24 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (6 RCTs; N=362)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>RR 0.82 (0.57 to 1.16)</td>
<td>Low</td>
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<tr>
<td>Leaving the study early (25-36 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (2 RCTs; N=90)</td>
<td>High</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>RR 0.59 (0.24 to 1.49)</td>
<td>Insufficient</td>
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<tr>
<td>Leaving the study early after 3 years</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=63)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>RR 1.72 (0.71 to 4.16)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Strength of Evidence Domain: Study Limitations</td>
<td>Strength of Evidence Domain: Consistency</td>
<td>Strength of Evidence Domain: Directness</td>
<td>Strength of Evidence Domain: Precision</td>
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<tr>
<td>Poor compliance with medication</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (4 RCTs; N=174) plus 2 RCTs; N=256</td>
<td>Moderate Consistent Indirect Imprecise</td>
<td>RR 0.78 (0.65 to 0.92)</td>
<td>Low</td>
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<tr>
<td>Relapse 0-6 months</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (2 RCTs; N=167)</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 0.62 (0.41 to 0.92)</td>
<td>Low</td>
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<tr>
<td>Relapse (7-12 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (16 RCTs; N=861) plus 4 RCTs; N=314</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 0.67 (0.54 to 0.83)</td>
<td>Moderate</td>
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<tr>
<td>Relapse (13-24 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (9 RCTs; N=517)</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 0.75 (0.58 to 0.99)</td>
<td>Low</td>
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<tr>
<td>Relapse (25-36 months)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (2 RCTs; N=147)</td>
<td>Moderate Inconsistent Direct Imprecise</td>
<td>RR 1.05 (0.80 to 1.39)</td>
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<tr>
<td>Relapse (5 years)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=63) plus 1 RCT; N=77</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>RR 0.82 (0.72 to 0.94)</td>
<td>Low</td>
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<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Strength of Evidence Domain: Study Limitations</td>
<td>Strength of Evidence Domain: Consistency</td>
<td>Strength of Evidence Domain: Directness</td>
<td>Strength of Evidence Domain: Precision</td>
<td>Magnitude of Effect: Summary (95% CI)</td>
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<tr>
<td>Relapse (8 years)</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=62)</td>
<td></td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>RR 0.86 (0.71 to 1.05)</td>
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<tr>
<td>Family Burden Not Improved or Worse</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (1 RCT; N=51)</td>
<td></td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Social functioning: RR 2.40 (0.51 to 11.27) at 1 year&lt;br&gt;RR 2.88 (0.64 to 12.97) at 2 years&lt;br&gt;Subjective burden: RR 1.44 (0.60 to 3.46) at 1 year&lt;br&gt;RR 0.58 (0.15 to 2.16) at 2 years</td>
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<tr>
<td>Nonsuicide mortality</td>
<td>Family intervention vs. usual care</td>
<td>1 SR (3 RCTs; N=113)</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>RR 0.96 (0.17 to 5.33)</td>
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</table>

EUROQOL=European Quality of Life scale, MD=mean difference, RR=relative risk, RCT=randomized controlled trial, SMD=standard mean difference, SR=systematic review.
### Intensive case management

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Strength of Evidence Domain: Study Limitations</th>
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<th>Strength of Evidence Domain: Directness</th>
<th>Strength of Evidence Domain: Precision</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
<th>Strength of Evidence (High, Moderate, Low, Insufficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Intensive case management vs. usual care</td>
<td>1 SR (3 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Pooled mean difference 0.46 (-0.34 to 0.126); one subsequent trial also found no difference using a different scale</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 RCT; N=77</td>
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<tr>
<td><strong>Quality of Life</strong></td>
<td>Intensive case management vs. usual care</td>
<td>1 SR (2 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Pooled mean difference 0.09 (-0.23 to 0.42); one subsequent trial also found no difference between groups in quality of life using a different scale</td>
<td>Insufficient</td>
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<tr>
<td></td>
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<td>1 RCT; N=77</td>
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<tr>
<td><strong>Overall Symptoms</strong></td>
<td>Intensive case management vs. usual care</td>
<td>1 SR (2 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Pooled mean difference 0.46 (-3.67 to 4.60); one subsequent trial also reported no difference.</td>
<td>Low</td>
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<tr>
<td></td>
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<td>1 RCT; N=77</td>
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<tr>
<td><strong>Loss to Follow-up</strong></td>
<td>Intensive case management vs. usual care</td>
<td>1 SR (7 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Less loss to follow-up with intensive case management compared to usual care: OR 0.70 (0.54 to 0.90)</td>
<td>Moderate</td>
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<tr>
<td></td>
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<td>1 RCT; N=77</td>
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<tr>
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<td>Imprisonment</td>
<td>Intensive case management vs. usual care</td>
<td>1 SR (5 RCTs)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No significant differences in imprisonment: OR 0.90 (0.45 to 1.82)</td>
<td>Low</td>
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</table>

**Illness management and recovery**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
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<th>Strength of Evidence (High, Moderate, Low, Insufficient)</th>
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<tbody>
<tr>
<td>Functioning</td>
<td>Illness self-management/self-management education intervention vs. usual care</td>
<td>1 SR (10 RCTs; N=409) plus 1 RCT; N=210</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Heterogeneous methods for measuring various types of functioning were used, with 5 finding benefit ad 6 not.</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
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<td>Number of Subjects</td>
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<tr>
<td>Symptoms</td>
<td>Illness self-management/self-management education intervention vs. usual care</td>
<td>1 SR (5 RCTs; N=409)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>BPRS (n=409), WMD: -4.19 (-5.84 to -2.54)</td>
<td>Moderate</td>
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<tr>
<td>Negative Symptoms</td>
<td>Illness self-management/self-management education intervention vs. usual care</td>
<td>1 SR (3 RCTs; N=257)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>PANSS negative -4.01 (-5.23 to -2.79)</td>
<td>Low</td>
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<td>Outcome</td>
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<tr>
<td>Relapse</td>
<td>Illness self-management/self-management education intervention vs. usual care</td>
<td>1 SR (3 RCTs; N=534)</td>
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<tr>
<th>Strength of Evidence Domain: Study Limitations</th>
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<th>Strength of Evidence Domain: Precision</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Relapse (&gt;10 interventions): N=233, OR 0.41 (0.21-0.79), p=0.008 Relapse (&lt;10 interventions): N=269, OR 0.67 (0.39-1.15), p=0.014</td>
</tr>
</tbody>
</table>

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, OR=odds ratio, PANSS=Positive and Negative Syndrome Scale, RCT=randomized controlled trial, SR=systematic review, WMD=weighted mean difference
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<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Global Functioning (GAF/GAS) at end of intervention</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=41)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -2.64 (-12.74 to 7.46)</td>
<td>Insufficient</td>
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<tr>
<td>Global Functioning (GAS) at 6 months</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=92)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Risk Ratio 0.83 (0.50 to 1.38)</td>
<td>Insufficient</td>
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<tr>
<td>Global Functioning (GAF/GAS) at 1 year</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (3 RCTs; N=260)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>MD -5.23 (-8.76 to -1.71), I² 79%</td>
<td>Low</td>
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<tr>
<td>Global Functioning (GAS) at 18 months</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=92)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Risk Ratio 0.90 (0.58 to 1.39)</td>
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<td>Outcome</td>
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<tr>
<td>Global Functioning (GAF/GAS) at 2 years</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=59)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -6.70 (-13.38 to 0.02)</td>
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<tr>
<td>Global Functioning (GAF/GAS) at 5 years</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=60)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -3.80 (-8.04 to 0.44)</td>
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<tr>
<td>Social Functioning (SAS-II) at end of intervention</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=19)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -0.10 (-0.37 to 0.17)</td>
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<tr>
<td>Quality of Life (Heinrich's Scale) at end of intervention</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=114)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>MD -8.20 (-14.78 to -1.62)</td>
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<tr>
<td>Quality of Life (Heinrich’s Scale) at 3 months</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=108)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>MD -9.70 (-17.22 to -2.18)</td>
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<tr>
<td>Outcome</td>
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<td>Number of Studies</td>
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<tr>
<td>BPRS at 3 months</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=19)</td>
<td></td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -0.06 (-0.53 to 0.41)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>BPRS at 1 year</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=159)</td>
<td></td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>MD -6.0 (-9.15 to -2.85)</td>
<td>Insufficient</td>
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<tr>
<td>Relapse with or without readmission: 9 to 18 Months</td>
<td>1 SR (6 RCTs; N=720)</td>
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<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Risk ratio 0.80 (0.70 to 0.92), I² 54%</td>
<td>Moderate</td>
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<tr>
<td>Relapse without readmission: total</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (3 RCTs; N=385)</td>
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<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: risk ratio 1.05 (0.84 to 1.31), I² 60%</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
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<td>Number of Studies</td>
<td>Number of Subjects</td>
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<tr>
<td>Relapse Without Readmission: 1 Year</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (2 RCTs; N=303)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: risk ratio 1.16 (0.92 to 1.46), I² 0.0%</td>
<td>Low</td>
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<tr>
<td>Relapse Without Readmission: 18 months</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (1 RCT; N=382)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: risk ratio 0.5 (0.23 to 1.11)</td>
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<tr>
<td>Harms: mortality</td>
<td>Psychoeducation vs. standard care</td>
<td>1 SR (2 RCTs; N=170)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: risk ratio 0.53 (0.07 to 3.95), I² 0.0%</td>
<td>Low</td>
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</tbody>
</table>

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, GAF =Global Assessment Functioning, GAS=Global Assessment Scale, MD=mean difference, RCT=randomized controlled trial, SAS=social adjustment score, SR=systematic review
### Social skills training

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Strength of Evidence Domain: Study Limitations</th>
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<th>Strength of Evidence Domain: Directness</th>
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</thead>
<tbody>
<tr>
<td>Function</td>
<td>Social skills training vs. usual care</td>
<td>3 RCTs (4 publications); N=384</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Significant improvement in scale scores during treatment for 6 months to 2 years (SMD 0.65 to 1.60)</td>
<td>Low</td>
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<tr>
<td>Function</td>
<td>Social skills training vs. usual care</td>
<td>1 RCT; N=183</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Social function not different from control after treatment cessation (1 study; SMD 0.24, 95% CI -0.05 to 0.53)</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
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<tr>
<td><strong>Overall Symptoms</strong></td>
<td>Social skills training vs. usual care</td>
<td>2 RCT; N=201</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Inconclusive: PANSS: SMD -1.50 (-1.92 to -1.09) and -0.81 (-1.22 to -0.40) BPRS (mixed population): SMD -0.04 (-0.33 to 0.25)</td>
<td>Low</td>
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<tr>
<td><strong>Overall Symptoms</strong></td>
<td>Social skills training vs. usual care</td>
<td>1 RCT; N=183</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>Inconclusive: Mixed population (55% schizophrenia), no significant effect on symptoms (BPRS): SMD -0.04 (-0.33 to 0.25)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparators</td>
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<td>Number of Subjects</td>
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<tr>
<td><strong>Negative Symptoms</strong></td>
<td>Social skills training vs. usual care</td>
<td>3 RCTs (4 publications); N=384</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Negative symptoms improved with social skills training vs. usual care based on PANSS-negative and SANS: SMD range -0.45 to -1.30 at 6 months to 2 years</td>
<td>Low</td>
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<tr>
<td><strong>Negative Symptoms</strong></td>
<td>Social skills training vs. usual care</td>
<td>1 RCT; N=183</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Negative symptoms were better with social skills training than usual care 1 year after treatment discontinuation: SMD - 0.45 (-0.74 to -0.15)</td>
<td>Insufficient</td>
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<tr>
<td><strong>Ability to Maintain Treatment</strong></td>
<td>Social skills training vs. usual care</td>
<td>2 RCTs; N=384</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>No difference: 1 year: RR 1.10 (0.92 to 1.31) 2 year: RR 1.01 (0.88 to 1.16)</td>
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<tr>
<td>Relapse</td>
<td>Social skills training vs. usual care</td>
<td>1 RCT; N=82</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.50 (0.18 to 1.36)</td>
<td>Insufficient</td>
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</table>

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, PANSS=Positive and Negative Syndrome Scale, RCT=randomized controlled trial, RR=relative risk, SANS=Scale for Assessment of Negative Symptoms, SMD=standard mean difference

### Supported employment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
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</thead>
<tbody>
<tr>
<td>Functional (occupational) - # in competitive employment</td>
<td>IPS vs. standard services</td>
<td>1 trial; N=204</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>75% vs. 27.5% (p&lt;0.001)</td>
<td>Low</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
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<tr>
<td>Functional (occupational) - # in competitive employment</td>
<td>Supported Employment (primarily IPS) vs. vocational training or usual care</td>
<td>1 RCT; N=1,273</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect for this review question</td>
<td>Precise</td>
<td>IPS vs. vocational training or usual care: 55% vs 34% (p&lt;0.001) Subgroup analysis of only patients with schizophrenia: 22% vs. 12%, p&lt;0.001 with mixed effects logistic regression</td>
<td>Moderate</td>
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<tr>
<td>Functional (occupational) - # in competitive employment</td>
<td>All comparators</td>
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<td></td>
<td></td>
<td>Moderate</td>
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<tr>
<td>Functional (occupational) - Days to first competitive employment</td>
<td>IPS vs. standard services</td>
<td>1 trial; N=204</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Days to first job: 196.63 vs. 218.84, p=0.019</td>
<td>Low</td>
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<tr>
<td>Functional (occupational) – Worked more than 20 hours per week</td>
<td>IPS vs. standard services</td>
<td>1 trial; N=204</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Worked &gt; 20 hours per week: 33.8% vs 13%, p=0.001</td>
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<tr>
<td>Functional (occupational) – Worked more than 20 hours per week</td>
<td>Supported Employment (primarily IPS) vs. vocational training or usual care</td>
<td>1 RCT; N=1,273</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect for this review question</td>
<td>Precise</td>
<td>IPS vs. vocational training or usual care Working &gt; 40 hours per month: 51% vs. 39%, p&lt;0.001</td>
<td>Moderate</td>
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<tr>
<td>Functional (occupational) – Worked more than 20 hours per week</td>
<td>All comparators</td>
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<td>Moderate</td>
</tr>
<tr>
<td>Functional (occupational) – Wages earned</td>
<td>IPS vs. standard services</td>
<td>1 trial; N=204</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>$2,078/month vs. $617.59/month, p&lt;0.001</td>
<td>Low</td>
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<td>Outcome</td>
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<td>Functional (occupational) – Wages earned</td>
<td>Supported Employment (primarily IPS) vs. vocational training or usual care</td>
<td>1 RCT; N=1,273</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect for this review question</td>
<td>Precise</td>
<td>IPS vs. vocational training or usual care</td>
<td>$122/month vs. $99/month, p=0.04</td>
<td>Moderate</td>
</tr>
<tr>
<td>Functional (occupational) – Wages earned</td>
<td>All comparators</td>
<td></td>
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<td>Moderate</td>
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<tr>
<td>Functional (occupational) – Weeks worked (mean)</td>
<td>IPS vs. standard services</td>
<td>1 trial; N=204</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Total weeks worked: 29.72 vs. 5.45, p&lt;0.001</td>
<td>Low</td>
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<tr>
<td>Functional (occupational) – Weeks worked (mean)</td>
<td>Supported Employment (primarily IPS) vs. vocational training</td>
<td>1 SR; N=2,265</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Indirect for this review question</td>
<td>Precise</td>
<td>Supported Employment vs. vocational training</td>
<td>Days employed: mean difference 70.63 (43.22 to 98.04)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Functional (occupational) – Weeks worked (mean)</td>
<td>All comparators</td>
<td></td>
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<td>Moderate</td>
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### Supportive therapy

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<thead>
<tr>
<th>Outcome</th>
<th>Comparators</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Strength of Evidence Domain: Study Limitations</th>
<th>Strength of Evidence Domain: Consistency</th>
<th>Strength of Evidence Domain: Directness</th>
<th>Strength of Evidence Domain: Precision</th>
<th>Magnitude of Effect: Summary Effect Size (95% CI)</th>
<th>Strength of Evidence (High, Moderate, Low, Insufficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Functioning</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (2 RCTs; N=289)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: GAF-M: MD -1.40(-5.09 to 7.89)</td>
<td>Low</td>
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<td>GAS: MD -2.66(-6.20 to 0.88)</td>
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<tr>
<td>Social Functioning</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (1 RCT; N=260)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: SFS: MD -0.67(-7.05 to 5.71)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
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<tr>
<td>Quality of Life</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (1 RCT; N=260)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RSES: MD -1.21 (-2.85 to 0.43) WBS: MD -2.73 (-6.04 to 0.58) GHQ: MD -2.45 (-2.41 to 7.31)</td>
<td>Insufficient</td>
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<tr>
<td>Relapse</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (1 RCT; N=54)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Medium term follow-up (13 to 26 weeks): RR 0.12 (0.01 to 2.11); Long-term follow-up (more than 26 weeks): RR 0.96 (0.44 to 2.11)</td>
<td>Insufficient</td>
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<tr>
<td>Outcome</td>
<td>Comparators</td>
<td>Number of Studies</td>
<td>Strength of Evidence Domain: Study Limitations</td>
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<tr>
<td>Core Symptoms</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (2 RCTs; N=167)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: PANSS: Short-term (13 to 26 weeks, n=131): MD -4.42 (-10.13 to 1.29); Long-term (more than 26 weeks, n=36): MD 4.70 (-6.71 to 16.11)</td>
<td>Insufficient</td>
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<tr>
<td>Negative Symptoms</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (1 RCT; N=47)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: Short-term: mean 10.19 vs. 10.73; Long-term: mean 9.90 vs. 11.46 (no statistical analysis because of skewed data)</td>
<td>Insufficient</td>
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## Early interventions for patients with first-episode psychosis

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</thead>
<tbody>
<tr>
<td>Discontinuing Treatment</td>
<td>Supportive therapy vs. standard care</td>
<td>1 SR (4 RCTs; N=354)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 0.86 (0.53 to 1.40)</td>
<td>Low</td>
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<tr>
<td>Functional: Global (GAS, GAF)</td>
<td></td>
<td>1 SR (1 RCT; N=369, two-year data only) plus 2 RCTs; N=744, N=98</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>GAS and GAF results only Team-based CSC resulted in higher functioning scores. Pooled WMD: 3.88 (0.91 to 6.85), I²=64%</td>
<td>Moderate</td>
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<tr>
<td><strong>Functional: Working or School</strong></td>
<td>1 SR (1 RCT; OPUS-Scandinavia) N=547) plus 2 RCTs; N=744, N=125</td>
<td>Moderate Consistent Direct Precise</td>
<td>Significantly more people (22%) are working or in school with team-based CSC. Pooled RR 1.22 (1.01 to 1.47)</td>
<td>Moderate</td>
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<tr>
<td><strong>Functional: Housing Status</strong></td>
<td>1 SR (1 RCT; N=547) plus 1 RCT; N=128</td>
<td>Moderate Consistent Direct Imprecise</td>
<td>No significant difference between groups Pooled RR 1.06 (0.86 to 1.30)</td>
<td>Moderate</td>
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<tr>
<td><strong>Health-Related Quality of Life</strong></td>
<td>2 RCTs; N=92, N=403</td>
<td>Moderate Consistent Direct Precise</td>
<td>Team-based CSC resulted in greater quality of life ratings as endpoint. Pooled effect size 0.84 (0.14 to 1.55), p=0.02 Cochrane Q for heterogeneity =7.43, p=0.0064 (significant heterogeneity)</td>
<td>Moderate</td>
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<tr>
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<tr>
<td>Core Illness Symptoms (PANSS)</td>
<td>3 RCTs; N=99, N=403, N=1,184</td>
<td></td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Precise</td>
<td>No clinically important difference between groups in endpoint scores: Pooled WMD of all 3 RCTs -2.53 (-5.45 to 0.39), $I^2 = 55%$ Sensitivity analysis removing a study with a 5.9-point difference at baseline resulted in a very small but statistically significant difference and no heterogeneity: Pooled WMD of 2 RCTs -1.40 (-2.25 to -0.55); Cochrane Q for heterogeneity = 0.0014 (df=1), $p=0.97$</td>
<td>Low</td>
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<tr>
<td>Core Illness Symptoms (Calgary Depression Scale)</td>
<td>2 RCTs; N=99, N=205</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td></td>
<td>No significant difference between groups in endpoint scores: Pooled WMD -0.44 (-1.08 to 0.20); Heterogeneity: Cochrane Q = 0.528157 (df = 1), $p=0.4674$</td>
<td>Moderate</td>
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<tr>
<td>Outcome</td>
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<tr>
<td>Discontinuation of Treatment</td>
<td>2 RCTs; N=1,239, N=136</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Team-based CSC had a significantly greater rate of treatment retention compared to standard care: Pooled relative risk 1.27 (1.16 to 1.38); Cochrane Q = 0.03 (df = 1), p=0.86</td>
<td>High</td>
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<tr>
<td>Rates of Relapse</td>
<td>2 RCTs; N=1,239, N=122</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Participants in team-based CSC were significantly less likely to relapse than those in standard care: Pooled relative risk 0.64 (0.52 to 0.79), Cochrane Q = 0.024 (df = 1), p=0.88</td>
<td>Moderate</td>
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</tbody>
</table>

Cl=confidence interval, CSC=coordinated specialty care, GAF=Global Assessment of Functioning, GAS=Global Assessment Scale, PANSS=Positive and Negative Syndrome Scale, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference
<table>
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<tr>
<th>Outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 6 months)</td>
<td>1 SR (1 RCT; N=162)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD 1.10 (-1.58 to 3.78)</td>
<td>Low</td>
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<tr>
<td>Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 18 months)</td>
<td>1 SR (1 RCT; N=176)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD 1.00 (-1.58 to 3.58)</td>
<td>Low</td>
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<tr>
<td>Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 24 months)</td>
<td>1 SR (1 RCT; N=166)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD 1.70 (-1.18 to 4.58)</td>
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<tr>
<td>Outcome</td>
<td>Number of Studies</td>
<td>Strength of Evidence Domain: Study Limitations</td>
<td>Strength of Evidence Domain: Consistency</td>
<td>Strength of Evidence Domain: Directness</td>
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<td>Function: Global Function (Integrated models of care vs. treatment as usual: GAF: 30 months)</td>
<td>1 SR (1 RCT; N=164)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -0.60 (-3.56 to 2.36)</td>
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<td>Function: Global Function (Integrated models of care vs. treatment as usual: GAF: 36 months)</td>
<td>1 SR (1 RCT; N=170)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD 0.40 (-2.47 to 3.27)</td>
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<tr>
<td>Function: Global Function (Non-Integrated: mean RFS score; 6 months)</td>
<td>1 SR (1 RCT; N=50)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: MD -0.78 (-2.91 to 1.35)</td>
<td>Insufficient</td>
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<tr>
<td>Function: Global Function (Non-Integrated: mean RFS score; 6 months)</td>
<td>1 SR (1 RCT; N=29)</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>MD -2.67 (-5.28 to -0.06)</td>
<td>Insufficient</td>
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<tr>
<td>Ability to maintain treatment (6 months)</td>
<td>1 SR (3 RCTs; N=134)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.23 (0.73 to 2.06)</td>
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<tr>
<td>Ability to maintain treatment (18 months)</td>
<td>1 SR (3 RCTs; N=134)</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Inconclusive: RR 1.35 (0.83 to 2.19)</td>
<td>Insufficient</td>
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</tbody>
</table>

GAF=global assessment functioning, MD=mean difference, RCT=randomized controlled trial, RFS=role functioning score, SR=systematic review