

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

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Acknowledgements

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

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Undergoing Copyediting

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Acronyms/Abbreviations

ACT	Assertive community treatment	DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders</i> , 5th Edition
AHRQ	Agency for Healthcare Research and Quality	ECG	Electrocardiography
AIMS	Abnormal Involuntary Movement Scale	ECT	Electroconvulsive therapy
APA	American Psychiatric Association	ER	Extended release
ANCs	Absolute neutrophil counts	FDA	Food and Drug Administration
BAP	British Association for Psychopharmacology	FGA	First-generation antipsychotic
BMI	Body mass index	GAF	Global Assessment of Functioning
BPRS	Brief Psychiatric Rating Scale	GRADE	Grading of Recommendations Assessment, Development and Evaluation
CATIE	Clinical Antipsychotic Trials for Intervention Effectiveness	HIPAA	Health Insurance Portability and Accountability Act
CBT	Cognitive-behavioral therapy	HIV	Human immunodeficiency virus
CBTp	Cognitive-behavioral therapy for individuals with psychosis	HR	Hazard ratio
CDC	Centers for Disease Control and Prevention	ICD	International Classification of Disease
CGI	Clinical Global Impression	IPS	Individual placement and support
CI	Confidence interval	LAI	Long-acting injectable
CrI	Credible interval	MD	Mean difference
CSC	Coordinated specialty care	NICE	National Institute for Health and Care Excellence
CSG	Canadian Schizophrenia Guidelines	NMS	Neuroleptic malignant syndrome
CYP	Cytochrome P450	NNH	Number needed to harm
DISCUS	Dyskinesia Identification System - Condensed User Scale	NNT	Number needed to treat
DSM	<i>Diagnostic and Statistical Manual of Mental Disorders</i>	NQF	National Quality Forum
		OR	Odds ratio
		PANSS-6	Positive and Negative Syndrome Scale, 6 item version

PANSS-30	Positive and Negative Syndrome Scale, 30 item version	SGA	Second-generation antipsychotic
PORT	Schizophrenia Patient Outcomes Research Team	SIGN	Scottish Intercollegiate Guidelines Network
PROMIS	Patient-Reported Outcomes Measurement Information System	SMD	Standardized mean difference
RAISE	Recovery After Initial Schizophrenia Episode	SOE	Strength of evidence
RANZCP	Royal Australian and New Zealand College of Psychiatry	SOFAS	Social and Occupational Functioning Assessment Scale
RCT	Randomized controlled trial	TdP	Torsades de pointes
REMS	Risk Evaluation and Mitigation Strategy	TMS	Transcranial magnetic stimulation
RR	Risk ratio or relative risk	TRRIP	Treatment Response and Resistance in Psychosis
SANS	Scale for the Assessment of Negative Symptoms	VMAT2	Vesicular monoamine transporter2
SAPS	Scale for the Assessment of Positive Symptoms	WFSBP	World Federation of Societies of Biological Psychiatry
SD	Standard deviation	WHODAS 2.0	World Health Organization Disability Schedule 2.0
SFS	Social Functioning Scale	WHOQOL-BREF	World Health Organization Quality of Life scale
		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 2009a), 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 (Plana-Ripoll et al. 2019), including substance use disorders (Hunt et al. 2018), contributes to morbidity and mortality among individuals with schizophrenia. About 4%-10% of persons with schizophrenia die by suicide, with rates that are highest among males in the early course of the disorder (Drake et al. 1985; Heilä et al. 2005; Hor and Taylor 2010; Inskip et al. 1998; Laursen et al. 2014; Nordentoft et al. 2011; Palmer et al. 2005; Popovic et al. 2014; Saha et al. 2007; Tanskanen et al. 2018). 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 and malignancies, particularly lung cancer (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 treatment for physical conditions

(Bergamo et al. 2014; DeHert et al. 2011; Druss et al. 2000; Janssen et al. 2015; Kisely et al. 2007, 2013; Kugathasan et al. 2018; Lawrence et al. 2010; Moore et al. 2015). Lack of access to adequate psychiatric treatment may also influence mortality (Schoenbaum et al. 2017).

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 based on its methodological rigor and adherence to accepted standards for systematic reviews.

This guideline is focused on the treatment of patients with schizophrenia and, as such, the statements in this guideline will be relevant to individuals with a diagnosis of schizophrenia. 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. Consequently, discussion of treatment, particularly treatment of first-episode psychosis, may also be relevant to individuals with schizophreniform disorder.

Although many of the studies included in the systematic review also included individuals with a diagnosis of schizoaffective disorder, these data were rarely analyzed separately in a way that would permit unique recommendations to be crafted for this group of patients. In addition, this guideline does not address issues related to identification or treatment of attenuated psychosis syndrome or related syndromes of high psychosis risk, which were not part of the AHRQ systematic review.

Data 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 including individuals being treated using integrated collaborative care models or inpatient or outpatient medical settings. Although treatment-related costs are often barriers to receiving treatment and cost-effectiveness considerations are relevant to health care policy, 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) and *the Principles for the Development of Specialty Society Clinical Guidelines* of the Council of Medical Specialty Societies (2012). Parameters used for the guideline's systematic review are included with the full text of the guideline; the 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 type and strength of the available evidence as well as the factors, including patient preferences, that were used in determining the balance of benefits and harms.

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

Pharmacotherapy

4. APA recommends (1A) that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.*
5. APA recommends (1A) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.*
6. APA suggests (2B) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.*
7. APA recommends (1B) that patients with treatment-resistant schizophrenia be treated with clozapine.*
8. APA recommends (1B) that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*
9. APA suggests (2C) that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.*
10. APA suggests (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*
11. APA recommends (1C) that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.

12. APA suggests (2C) the following options for patients who have parkinsonism associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.
13. APA suggests (2C) the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.
14. APA recommends (1B) that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter2 (VMAT2).

Psychosocial Interventions

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

*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: Assessment of Possible Schizophrenia

APA recommends (1C) that the initial assessment of a patient with a possible psychotic disorder include the reason the individual is presenting for evaluation, the patient's goals and preferences for treatment, a review of psychiatric symptoms and trauma history, an assessment of tobacco use and other substance use, a psychiatric treatment history, an assessment of physical health, an assessment of psychosocial and cultural factors, a mental status examination including cognitive assessment, and an assessment of risk of suicide and aggressive behaviors, as outlined in APA's Practice Guidelines for the Psychiatric Evaluation of Adults (3rd edition).

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 2016a) 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. In many circumstances, aspects of the evaluation will extend across multiple visits (American Psychiatric Association 2016a).

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:
 - Hallucinations (including command hallucinations), delusions, and negative symptoms
 - 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., vaping, 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 hallucinations, delusions, negative symptoms, and insight
- Cognition
- Current suicidal ideas, suicide plans, and suicide intent, including active or passive thoughts of suicide or death
 - 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
 - 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

The specific approach to the interview will depend on many factors, including the patient's ability to communicate, degree of cooperation, level of insight, illness severity, and ability to recall historical details (American Psychiatric Association 2016a). 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 2016a). 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.

Throughout the assessment process, it is important to gain an understanding of the patient's goals, their view of their illness, and their preferences for treatment. This information will serve as a starting point for person-centered care and shared decision-making with the patient, family, and other persons of support (Dixon et al. 2016; Hamann and Heres 2019). It will also provide a framework for recovery, which has been defined as "a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential." (Substance Abuse and Mental Health Services Administration 2012a). Consequently, discussions of goals should be focused beyond symptom relief and may include goals related to schooling, employment, living situation, relationships, leisure activities, and other aspects of functioning and quality of life. Questions about the patient's views may help determine whether the patient is aware of having an illness and whether the patient has other explanations for symptoms that are helpful to them (Saks 2009). Patients may have specific views about topics such as medications, other treatment approaches, mechanical restraints, or involuntary treatment based on prior treatment experiences. They may also be able to delineate strategies that have been helpful for them in coping with or managing their symptoms in the past (Cohen et al. 2017). Some patients will have completed a psychiatric advance directive (Murray and Wortzel 2019), which is important to review with the patient if it exists.

In addition to direct interview, patients may be asked to complete electronic- or paper-based forms that ask about psychiatric symptoms or key aspects of the history (American Psychiatric Association 2016a). 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 2016a).

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 2016a). 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 (U.S. Department of Health and Human Services; Office for Civil Rights 2017b). For example, if a relative or person of support 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 2016a). 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) (U.S. 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 as well as to jails, prisons, and law enforcement officials having lawful custody of 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 (U.S. 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, many features and aspects of clinical course will enter into such a determination in addition to psychotic symptoms, per se. Clinicians should also be mindful that biases can influence assessment and diagnosis, with disparities in diagnosis based on race being particularly common (Olbert et al. 2018; Schwartz and Blankenship 2014). The clinician should be alert to features of the history, including family, developmental, and academic history, that may suggest specific conditions or a need for additional physical or laboratory evaluation. Examples of conditions that can mimic schizophrenia in their initial presentation include neurosyphilis, Huntington's disease, Wilson's disease, or anti-NMDA receptor encephalitis (Lieberman and First 2018). Individuals with 22q11.2 deletion syndrome have a substantially increased risk of developing schizophrenia (Bassett et al. 2017; McDonald-McGinn et al. 2015; Van et al. 2017). In addition, the presence of a 22q11.2 deletion is associated with an increased likelihood of neurocognitive and physical health impairments (McDonald-McGinn et al. 2015; Moberg et al. 2018; Swillen and McDonald-McGinn 2015), which has implications for treatment (Fung et al. 2015; Mosheva et al. 2019). 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). Specialty consultation can be helpful in establishing and clarifying diagnosis (Coulter et al. 2019), particularly if the illness symptoms or course appear to be atypical or if the patient is not responding to treatment.

A thorough history is also important to identify the presence of co-occurring psychiatric conditions or physical disorders that need to be addressed in treatment planning (American Psychiatric Association 2016a; Firth et al. 2019). For example, 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). Furthermore, 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 2016a; Large et al. 2014). Thus, as part of the initial evaluation, it is important to determine whether the patient uses tobacco, cannabis, or other substances such as alcohol, caffeine, cocaine, opioids, sedative-hypnotic agents, stimulants, 3,4-methylenedioxy-methamphetamine (MDMA), solvents, androgenic steroids, hallucinogens, or synthetic substances (e.g., "bath salts", K2, Spice). The route by which substances are used (e.g., ingestion, smoking, vaping, intranasal, intravenous) is similarly important to document.

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). Adverse health effects of smoking also contribute to an increased risk of mortality among individuals with schizophrenia (Lariscy et al. 2018; Reynolds et al. 2018; Tam et al. 2016). 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); cancer (Olfson et al. 2015); 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 some 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

Assessments to monitor physical status and detect concomitant physical conditions		
Assessment	Initial or Baseline^a	Follow-Up^b
Vital signs	Pulse, blood pressure	Pulse; blood pressure; temperature as clinically indicated
Body weight and height	Body weight, height, and BMI ^c	BMI ^c every visit for 6 months and at least quarterly thereafter
Hematology	CBC, including ANC	CBC, including ANC if clinically indicated (e.g., patients treated with clozapine)
Blood chemistries	Electrolytes Renal function tests Liver function tests TSH	As clinically indicated
Pregnancy	Pregnancy test for women of childbearing potential	
Toxicology	Drug toxicology screen, if clinically indicated	Drug toxicology screen, if clinically indicated
EEG	EEG, if indicated based on neurological exam or history	
Imaging	Brain imaging (CT or MRI, with MRI being preferred), if indicated based on neurological exam or history ^d	
Genetic testing	Chromosomal testing, if indicated based on physical exam or history, including developmental history ^e	

Table 2. Suggested physical and laboratory assessments for patients with schizophrenia (continued)

Assessments related to other specific side effects of treatment		
Assessment	Initial or Baseline^a	Follow-Up^b
Diabetes ^f	Screening for diabetes risk factors ^g ; fasting blood glucose ^h	Fasting blood glucose or hemoglobin A1c at 4 months after initiating a new treatment and at least annually thereafter ^h
Hyperlipidemia	Lipid panel ⁱ	Lipid panel at 4 months after initiating a new antipsychotic medication and at least annually thereafter
Metabolic syndrome	Determine if metabolic syndrome criteria are met. ^j	Determine if metabolic syndrome criteria are met ^j at 4 months after initiating a new antipsychotic medication and at least annually thereafter.
QTc prolongation	ECG before treatment with chlorpromazine, droperidol, iloperidone, pimozide, thioridazine, or ziprasidone ^k or in the presence of cardiac risk factors ^l	ECG with significant change in dose of chlorpromazine, droperidol, iloperidone, pimozide, thioridazine, or ziprasidone ^k , or with the addition of other medications that can affect QTc interval in patients with cardiac risk factors ^l or elevated baseline QTc intervals
Hyperprolactinemia	Screening for symptoms of hyperprolactinemia ^m Prolactin level, if indicated on the basis of clinical history	Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactin ^m Prolactin level, if indicated on the basis of clinical history

Antipsychotic-induced movement disorders	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia ⁿ Assessment with a structured instrument (e.g., AIMS, DISCUS) if such movements are present	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia, at each visit ⁿ Assessment with a structured instrument (e.g., AIMS, DISCUS) at a minimum of every 6 months in patients at high risk of tardive dyskinesia ^o and at least every 12 months in other patients ^p as well as if a new onset or exacerbation of pre-existing movements is detected at any visit
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Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ANC= absolute neutrophil count; BMI=body mass index; CBC=complete blood count; CT=computed tomography; DISCUS=Dyskinesia Identification System - Condensed User Scale; ECG=electrocardiography; EEG=electroencephalogram; MRI=magnetic resonance imaging; QTc=corrected QT interval; TSH=thyroid stimulating hormone

^aAPA's *Practice Guidelines for the Psychiatric Evaluation of Adults*, 3rd edition (American Psychiatric Association 2016a) 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.

^bAlthough 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.

^cBMI 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.

^d Factors that suggest a possible need for imaging include focal neurological signs; new onset of seizures; later age at symptom onset; symptoms suggestive of intracranial pathology (e.g., chronic or severe headaches, nausea, and vomiting); and symptoms suggestive of autoimmune encephalitis (e.g., rapid progression of working memory deficits over less than 3 months; decreased or altered level of consciousness, lethargy, or personality change; Graus et al. 2016). In the absence of such indications, decisions about imaging should consider that the yield of routine brain imaging is low, with less than 1% of studies showing potentially serious incidental findings or abnormalities that would influence treatment (Cunqueiro et al. 2019; Falkenberg et al. 2017; Forbes et al. 2019; Gibson et al. 2018). On the other hand, routine imaging is a low-risk procedure and a negative finding can be reassuring to patients and to families. If imaging is ordered, it is rarely necessary to delay other treatment or hospitalization while awaiting imaging results.

^e Factors that may suggest a possible need for chromosomal testing (e.g., to identify abnormalities such as 22q11.2 deletion syndrome) include mild dysmorphic features, hypernasal speech, developmental delays, intellectual impairments, learning difficulties, or congenital heart defects (Bassett and Chow 1999; Miller et al. 2010).

^f 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, including extreme hyperglycemia. In some patients, this hyperglycemia was associated with ketoacidosis, hyperosmolar coma, or death.

^g 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 ($\geq 140/90$ 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 Association 2018). Symptoms of possible diabetes include frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurry vision.

^h When screening for the presence of diabetes, criteria for diagnosis (American Diabetes Association 2018) include a fasting blood 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 blood glucose of at least 200 mg/dL in conjunction with a hyperglycemic 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 blood glucose should be used rather than hemoglobin A1C. An abnormal value of fasting blood 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.

ⁱ 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).

^jMetabolic syndrome is currently defined by the presence of at least 3 of the following 5 risk factors: Elevated waist circumference (defined for the U.S. and Canada as >102 cm [40.2 inches] for men and >88 cm [34.6 inches] for women); elevated triglycerides of ≥ 150 mg/dl (or drug treatment for elevated triglycerides, such as fibrates, nicotinic acid, or high dose omega-3 fatty acids); reduced high density lipoprotein cholesterol (HDL-C) of <40 mg/dL in men or < 50 mg/dL in women (or drug treatment for reduced HDL-C, such as fibrates or nicotinic acid), elevated blood pressure with systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg (or antihypertensive treatment in a patient with a history of hypertension); elevated fasting glucose ≥ 100 mg/dL (or drug treatment for elevated glucose). (Alberti et al. 2009).

^kUsing 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. 2009).

^lIn this context, risk factors include non-modifiable (e.g., congenital long QT syndrome, age, sex, family history of sudden cardiac death, personal or family history of structural or functional heart disease, personal history of drug-induced QT prolongation, metabolizer status) and modifiable risk factors (e.g., 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 drug-drug interactions, acute or chronic kidney disease, or hepatic impairment; Funk et al. 2018).

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

ⁿAssessment 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) or the Dyskinesia Identification System Condensed User Scale (DISCUS) (Kalachnik and Sprague 1993). For a copy of the AIMS scale, see: http://cqaimh.org/pdf/tool_aims.pdf and for a copy of the DISCUS, see <https://portal.ct.gov/-/media/DDS/Health/hcsma20002b.pdf>.

^oPatients at increased risk for developing abnormal involuntary movements include individuals older than 55 years; women; individuals with a mood disorder, substance use disorder, intellectual disability, or central nervous system injury; individuals with high cumulative exposure to antipsychotic medications, particularly high potency dopamine D2 receptor antagonists; and patients who experience acute dystonic reactions, clinically significant parkinsonism, or akathisia (Carbon et al. 2017, 2018; Miller et al. 2005; Solmi et al. 2018b). Abnormal involuntary movements can also emerge or worsen with antipsychotic cessation.

^pFrequency 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 2016a). 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, buprenorphine) 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.

The psychosocial history reviews the stages of the patient's life and may include attention to perinatal events, delays in developmental milestones, academic history and performance (including learning difficulties, special educational interventions, or disciplinary actions), relationship and sexual history, interpersonal functioning (including in social and family roles, such as parenting), occupational history (including military history), legal history, and identification of major life events (e.g., parental loss, divorce, traumatic experiences, migration history) and psychosocial stressors (e.g., financial, housing, legal, school/occupational, or interpersonal/relationship problems; lack of social support; painful, disfiguring, or terminal medical illness) (American Psychiatric Association 2016a; Barnhill 2014; MacKinnon et al. 2016; Smith et al. 2019). Information about the patient's family constellation and persons who provide support will serve as a foundation for working collaboratively with the patient and his or her support network. The cultural history also emphasizes relationships, both familial and nonfamilial, and the role of important cultural and religious influences on the patient's life (Aggarwal and Lewis-Fernández 2015; American Psychiatric Association 2013a; Lewis-Fernández et al. 2016).

The mental status examination is an integral part of the initial assessment. A full delineation of the mental status examination is beyond the scope of this document and detailed information on its conduct is available elsewhere (American Psychiatric Association 2016a; Barnhill 2014; MacKinnon et al. 2016; Smith et al. 2019; Strub and Black 2000). However, for individuals with possible schizophrenia, a detailed inquiry into hallucinations and delusions will often identify psychotic experiences in addition to the presenting concerns. Negative symptoms and cognitive impairment are common and influence outcomes (Bowie et al. 2006; Green 2016; Jordan et al. 2014; Rabinowitz et al. 2012; Santesteban-Echarri et al. 2017) but may go undetected without specific attention during the evaluation. Negative symptoms can also be difficult to differentiate from lack of interest or reduced motivation due to depression, medication side effects, substance use, or neurological conditions.

Insight is also impaired in a significant proportion of individuals with schizophrenia (Mohamed et al. 2009) and can manifest as a decreased awareness of having a disorder, symptoms, consequences of illness, or a need for treatment (Mintz et al. 2003). Consequently, inquiring about the patient's degree of insight and judgment will provide information relevant to risk assessment, treatment outcomes, and adherence (Mintz et al. 2003; Mohamed et al. 2009).

Risk assessment is another essential part of the initial psychiatric evaluation (American Psychiatric Association 2004). It requires synthesizing information gathered in the history and mental status examination and identifying modifiable risk factors for suicidal or aggressive behaviors that can serve as targets of intervention in constructing a plan of treatment. Suicidal ideas are common in individuals who have had a psychotic experience (Bromet et al. 2017). Death due to suicide has been estimated to occur in about 4%-10% of individuals with schizophrenia (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, 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, 2014). Firearm access is an additional contributor to suicide risk (Alban et al. 2018; Anestis et al. 2018; Siegel and Rothman 2016). Additional factors that have been identified as increasing risk for suicide among individuals with schizophrenia include depressive symptoms, hopelessness, agitation or motor restlessness, fear of mental disintegration, recent loss, recency of diagnosis or hospitalization, repeated hospitalizations, high intelligence, young age, and poor adherence to treatment (Cassidy et al. 2018; Hawton et al. 2005; Fleischhacker et al. 2014; Lopez-Morinigo et al. 2014; Pompili et al. 2007; Popovic et al. 2014; Randall et al. 2014). 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-Moríñigo 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 (McNiel 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 Nielszen 2011; Reagu et al. 2013; Swanson et al. 2006; Witt et al. 2013, 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, 2014; Fleischhacker et al. 2014; Large and Nielszen 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, 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. 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*, 3rd edition) 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*, 3rd edition (American Psychiatric Association 2016a). 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

* 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.

planning in individuals with a psychiatric disorder (for additional details, see American Psychiatric Association 2016a). (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 tobacco use (Addington et al. 2017a; 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 mental status examination (Addington et al. 2017a) including 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. A first step to development of scientifically sound quality measures is identification of discrete indicators that signal the delivery of high-quality care. This step may be challenging to accomplish given the breadth of content within the initial psychiatric assessment and the difficulty in ascertaining evaluation details from chart or administrative data. However, it may still be possible to use available evidence and expert-recommended consensus to develop and specify electronic and clinical data registry quality measures. Additionally, as discussed in the *APA Practice Guidelines for the Psychiatric Evaluation of Adults*, 3rd edition (American Psychiatric Association 2016a), 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: Use of Quantitative Measures

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

Implementation

APA's *Practice Guidelines for the Psychiatric Evaluation of Adults*, 3rd edition (American Psychiatric Association 2016a) 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 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. If a mismatch is noted in the self-assessment of patients as compared to assessments of other observers, this may provide information relevant to outcomes. The accuracy of self-assessments of ability, skills, performance, or decisions (also termed introspective accuracy) is a better predictor of everyday functional deficits than objective measures of neurocognitive or social cognitive performance (Silberstein and Harvey 2019.)

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 (Lewis et al. 2019). 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 Scale for 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 2000a) and the Personal and Social Performance scale (Morosini et al. 2000). Several versions of Patient-Reported Outcomes Measurement Information System (PROMIS) scales are also available that address social roles and functioning (www.healthmeasures.net/explore-measurement-systems/promis). 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).

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) (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. Reviewing scale results with the patient can help foster a collaborative dialogue about progress toward symptom improvement, functioning gains, and recovery goals. Such review may help clinicians, patients, families, and other support persons recognize that improvement is taking place or, conversely, identify issues that need further attention.

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 (Lewis et al. 2019; Palmier-Claus et al. 2012; K. Wang et al. 2018). 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. Although mobile apps may be capable of assisting with quantitative measurement, there is no current evidence on which to base recommendations about use of mobile apps in the treatment of schizophrenia.

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.

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*, 3rd edition (American Psychiatric Association 2016a). 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*, 3rd edition; American Psychiatric Association 2016a).

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, 2017c; Barnes et al. 2011; Buchanan et al. 2010; Crockford and Addington 2017; Hasan et al. 2012, 2013, 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

There is insufficient consensus on the most appropriate quantitative measures (i.e., rating scales) to use in assessing individuals with psychotic disorders, including schizophrenia. Nevertheless, there is data supporting the use of clinician-reported, symptom-based ratings to guide treatment. Patient-rated scales may be clinically useful in identifying patient concerns or subjective experiences (e.g., medication side effects). On the basis of these potential benefits, 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: Evidence-based Treatment Planning

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 with the patient 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, impairments in insight, changes in presenting issues or symptoms, or revisions in diagnosis. 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. For most individuals with schizophrenia, it is challenging to piece together a coherent picture of the patient's longitudinal course from medical records. Thus, 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.

Aims of 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. Depending on prevailing state laws, psychiatric advance directives are one approach to encouraging patients to contemplate and state their preferences about treatment choices (Easter et al. 2017; Kemp et al. 2015; Shields et al. 2014; Wilder et al. 2010). For patients who have completed a psychiatric advance directive, wellness recovery action plan (Copeland 2000), or individualized crisis prevention or safety plan (Safety Planning Intervention 2018; Stanley and Brown 2012; Stanley et al. 2018), these documents will be important to review with 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, using shared decision-making whenever possible. 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 lack of insight, cognitive impairments, disorganization, or inadequate social resources.

Elements of the Treatment Plan

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, including peer-support programs
- 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 avoid fragmentation of treatment efforts and assure that co-occurring substance use disorders and physical health conditions are managed

Engagement of Family Members and Other Persons of Support

Discussions with the patient, family members, and others will typically occur as part of the initial assessment (see Statement 1) and additional input will be needed as treatment proceeds and the treatment plan is updated. 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. Most individuals welcome involvement of family members and other persons of support (Cohen et al. 2013; Drapalski et al. 2018; Mueser et al. 2015) and family members can be an important part of the care team. Family members can also be provided with educational materials or directed to organizations that offer education to family members and other persons of support (National Alliance on Mental Illness 2019; Mental Health America 2019).

Strategies to Promote Adherence

Strategies to promote adherence are always important to consider in developing a patient-centered treatment plan (Ferrando et al. 2014). Maintaining adherence to treatment is often challenging (Acosta et al. 2012; Shafrin et al. 2016; Valenstein et al. 2006) and poor adherence is associated with poor outcomes including increased risks of relapse, rehospitalization, suicidal and aggressive behaviors, and mortality (Bowtell et al. 2018; Cassidy et al. 2018; Goff et al. 2017; Hawton et al. 2005; Hui et al. 2018; Kishi et al. 2019; Leucht et al. 2012; Thompson et al. 2018; Tiihonen et al. 2018; Vermeulen et al. 2017; Witt et al. 2013). 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. Issues that may influence adherence include, but are not limited to, lack of awareness of illness, 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, effects on cognition), financial barriers (e.g., cost, insurance coverage), perceived risks and benefits of treatment, insufficient understanding of medication benefits for symptoms that are important to the patient, ambivalence or 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), high levels of hostility, persecutory delusions, prior difficulties with adherence, prior experiences with treatment (e.g., effectiveness, side effects), limited geographic availability or accessibility of services, financial or insurance constraints on medications or visits, difficulties in the therapeutic relationship, lack of support from significant others for treatment, cultural or family beliefs about illness or 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; Mueser et al. 2015; 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, difficulties scheduling visits around work or school schedules, or issues with transportation or with childcare. 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 (Mueser et al. 2015).

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). 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). It can also be useful to obtain medication blood levels. Levels of clozapine have been best studied but blood levels of other antipsychotic medications are also available. Although the utility of routine therapeutic monitoring is unclear for antipsychotic medications other than clozapine, blood levels may help in establishing whether a patient is taking the medication (Hiemke et al. 2018; Horvitz-Lennon et al. 2017; Lopez and Kane 2013; Lopez et al. 2017; McCutcheon et al. 2018; Predmore et al. 2018). Urine levels of antipsychotic medications can also be used to assess for adherence (Velligan et al. 2006).

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. 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). 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, adjusting dosing to minimize side effects while maintaining efficacy, 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; Hamann and Heres 2019; Kane et al. 2013; Rezanoff et al. 2017).

For some patients, the formulation of the antipsychotic medication may influence adherence (see Table 3, Statement 4). For example, rapid dissolving tablets, oral concentrates, or LAI formulations may be preferable for patients who have difficulty swallowing pills or who are ambivalent about medications and inconsistent in swallowing them. For individuals who have difficulty remembering to take medication, LAI formulations of medications can be used, oral 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. Behavioral tailoring is another approach that can be used to improve adherence and involves cuing oneself to take medications by incorporating adherence into one's daily routine (Kreyenbuhl et al. 2016; Mueser et al. 2002). 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.

Addressing Risks for Suicidal and Aggressive Behavior

Identifying risk factors and estimating risks for suicidal and aggressive behaviors are essential parts of psychiatric evaluation (American Psychiatric Association 2016a 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 re-evaluate the setting of care and implement approaches to target and reduce modifiable risk factors. Although demographic and historical risk factors are static, potentially modifiable risk factors may include poor adherence, core symptoms of schizophrenia (e.g., hallucinations, delusions), co-occurring symptoms (e.g., depression, hopelessness, hostility, impulsivity), and co-occurring diagnoses (e.g., depression, alcohol use disorder, other substance use disorders). Additional elements of the treatment plan can address periods of increased risk (e.g., shortly after diagnosis, during incarceration, subsequent to hospital discharge).

Addressing Tobacco Use and Other Substance Use Disorders

Individuals with schizophrenia have high rates of nicotine dependence (Centers for Disease Control and Prevention 2019b; Cook et al. 2014; de Leon and Diaz 2005; Dickerson et al. 2018; Hartz et al. 2014; Myles et al. 2012; Smith et al. 2014; Wium-Andersen et al. 2015), cannabis use (Brunette et al. 2018; Hartz et al. 2014; Hunt et al. 2018; Koskinen et al. 2010; Nesvåg et al. 2015; Toftdahl et al. 2016), and use of alcohol and other substances (Brunette et al. 2018; Hartz et al. 2014; Hunt et al. 2018; Nesvåg et al. 2015; Toftdahl et al. 2016). Smoking is a major contributor to increased mortality in individuals with serious mental illness (Reynolds et al. 2018; Tam et al. 2016) and the adverse health consequences of smoking are well documented (U.S. Department of Health and Human Services 2014; Van Schayck et al. 2017; Lariscy et al. 2018). Thus, smoking cessation is recommended for any individual who smokes. 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). Although quit rates may be lower in individuals with schizophrenia than in the general population (Lum et al. 2018; Streck et al. 2018), health education and motivational interviewing approaches can be helpful in those who are ambivalent about stopping cigarette use (Levounis et al. 2017) or who have had prior unsuccessful attempts at smoking cessation.

Rates of cannabis use and other substance use are also increased among individuals with schizophrenia (Hartz et al. 2014; Hunt et al. 2018; Swartz et al. 2006). Cannabis use has been associated with an increased incidence (Nielsen et al. 2017, Vaucher et al. 2018) and earlier onset (Donoghue et al. 2014; Helle et al. 2016; Kelley et al. 2016; Large et al. 2011) of schizophrenia and it may also contribute to a higher burden of symptoms (Carney et al. 2017; 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. Screening, brief intervention, and referral to treatment (SBIRT) can be integrated into a range of clinical settings (Agerwala and McCance-Katz 2012; SAMHSA-HRSA Center for Integrated Health Solutions 2019). Often, a comprehensive integrated treatment model is 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).

Addressing Other Concomitant Psychiatric Symptoms and Diagnoses

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. 2017b) 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). When anxiety symptoms are present 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. 2017b).

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.

Addressing Other Concomitant Health Conditions

As described in Statement 1, other health conditions are more frequent in individuals with serious mental illness in general (Firth et al. 2019; Janssen et al. 2015; McGinty et al. 2016) and schizophrenia in particular (Henderson et al. 2015). Such disorders include but are 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); HIV infection (Hobkirk et al. 2015; Hughes et al. 2016); cancer (Olfson et al. 2015); 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 some may be induced or exacerbated by psychiatric medications. Impairments in renal and hepatic function, if present, can influence treatment recommendations.

Table 2 of Statement 1 provides a discussion of suggested physical and laboratory assessments for patients with schizophrenia as part of initial evaluation and follow-up assessments. Such assessments are important to prevention, early recognition, and treatment of abnormalities such as glucose dysregulation, hyperlipidemia, and metabolic syndrome. 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 (American Psychiatric Association 2016a), but the psychiatrist may also provide ongoing monitoring and treatment of common medical conditions in conjunction with primary care clinicians (Druss et al. 2018).

Pregnancy and Post-partum

Women with childbearing potential and at risk for pregnancy should be assisted in obtaining effective contraception if pregnancy is not desired. For women who are planning to become pregnant or who are pregnant or in the post-partum period, it is essential to collaborate with the patient, her obstetrician-gynecologist or other obstetric practitioner, and, if involved, her partner or other persons of support. For women who are breastfeeding, collaboration with the infant's pediatrician is similarly important. The overall goal is to develop a plan of care aimed at optimizing outcomes for both the patient and her infant. In addition, during pregnancy and post-partum, frequent reassessment will be needed to determine whether any modifications to the treatment plan are indicated.

As with any decisions related to the use of psychiatric medications prior to conception, during pregnancy or while breastfeeding, it is essential to consider the potential benefits of treatment as well

as the potential harms of untreated illness and the potential for negative fetal or neonatal effects. Untreated or inadequately treated maternal psychiatric illness can result in poor adherence to prenatal care, inadequate nutrition, increased alcohol or tobacco use, and disruptions to the family environment and mother–infant bonding (ACOG Committee on Practice Bulletins—Obstetrics 2008; American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017; Tosato et al. 2017). For women with childbearing potential, decisions about medications and advice about contraceptive practices should consider the potential effects if pregnancy were to occur. Some medications are best avoided in women with childbearing potential with valproic acid being one example due to its teratogenic effects (Briggs et al. 2017) and association with maternal metabolic syndrome.

All psychotropic medications studied to date cross the placenta, are present in amniotic fluid, and enter human breast milk (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017). In addition, the period from the third through the eighth week of gestation is associated with greatest risk for teratogenesis (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017). If a woman becomes pregnant while taking an antipsychotic medication, consideration should be given to consulting an obstetrician–gynecologist or maternal–fetal medicine subspecialist in addition to discussion with the prescribing clinician before indicated psychotropic medications are stopped to determine whether the risks of stopping the medication outweigh any possible fetal risks (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017; U.S. Food and Drug Administration 2011). For many women, the eighth week of gestation will already have passed before obstetrical care begins and stopping medication will not avoid or reduce teratogenic risk. Thus, in a woman with schizophrenia, the benefits of continued treatment with antipsychotic medications in minimizing relapse will generally outweigh the potential for fetal risk (Briggs et al. 2017).

Knowledge of the effects of antipsychotic medications is limited to observational and registry-based studies. Although limited information is known about newer SGAs, first-generation antipsychotic medications (FGAs) have been in wide use for over 40 years and older SGAs have been available for several decades. The available data suggest that these medications have minimal risk in terms of teratogenic or toxic effects on the fetus (ACOG Committee on Practice Bulletins—Obstetrics 2008; Briggs et al. 2017; Chisolm and Payne 2016). There does appear to be a risk of withdrawal symptoms or neurological effects of antipsychotic medications in the newborn if an antipsychotic medication is used in the third trimester (Briggs et al. 2017; U.S. Food and Drug Administration 2011). Symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding (Briggs et al. 2017; U.S. Food and Drug Administration 2011). Nevertheless, tapering of antipsychotic medication late in pregnancy is not advisable due to the associated risk of relapse. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays (U.S. Food and Drug Administration 2011). The possibility of these effects signals the importance of close monitoring of the newborn in conjunction with the infant's pediatrician. As noted above, however, the benefits of treatment for the mother and the longer term benefits of treatment for the infant (e.g., enhanced

mother–infant bonding, better adherence to prenatal care and nutrition, lesser rates of prenatal alcohol or tobacco use) will generally favor continuing and not tapering antipsychotic treatment.

A number of other considerations are relevant when treating women with an antipsychotic medication during pregnancy. In general, symptoms should be managed with the lowest effective dose although it is preferable to maintain efficacy using a single medication at a higher dose rather than using multiple medications at lower doses (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017). If a patient's symptoms are well controlled on a specific medication, it is usually not advisable to switch to a different antipsychotic medication, even if more safety information is available for a different drug (Chisolm and Payne 2016). Changing medications exposes the fetus to two different medications and also increases the possibilities for symptom relapse in the patient.

Close monitoring for symptom recurrence and for side effects is important during pregnancy and in the postpartum period because the physiologic alterations of pregnancy may affect the absorption, distribution, metabolism, and elimination of medications and may necessitate adjustments in medication doses (ACOG Committee on Practice Bulletins—Obstetrics 2008; Chisolm and Payne 2016). Women who are taking antipsychotic medications are also at increased risk of obesity and hyperglycemia; folate supplementation to reduce risks of neural tube defects and assessment for diabetes during pregnancy will be important elements of prenatal care (Briggs et al. 2017). As with all women who are pregnant, regular prenatal care is essential to assuring optimal maternal-fetal outcomes (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists 2017; American College of Obstetricians and Gynecologists 2018).

In terms of breastfeeding, limited information is available, but infants may be exposed to clinically significant levels of medication in breast milk and the long-term effects of such exposure is not known (Sachs et al. 2013). Accordingly, mothers who wish to breastfeed their infants should review the potential benefits of breastfeeding as well as potential risks in the context of shared decision-making (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice; Breastfeeding Expert Work Group 2016; Sachs et al. 2013) with associated monitoring of growth and development by the infant's pediatrician (Sachs et al. 2013).

Additional information related to the use of antipsychotic medications during pregnancy and while breastfeeding can be found on the websites of the U.S. Food and Drug Administration (FDA) (www.fda.gov), RePROTOX (<http://www.reprotox.org/>), TERIS (www.depts.washington.edu/terisweb/teris/), and the U.S. National Library of Medicine's LactMed (<https://www.ncbi.nlm.nih.gov/books/NBK501922/>). For women who have been treated with an SGA during pregnancy, enrolling in the National Pregnancy Registry for Atypical Antipsychotics is suggested (MGH Center for Women's Mental Health 2019).

Determining a Treatment Setting

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. However, if hospitalization is deemed essential but not accepted voluntarily by the patient, state or jurisdictional requirements for involuntary hospitalization should be followed. 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 psychiatric or other medical 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.

For individuals with schizophrenia and other significant health issues, determination of a treatment setting will require weighing the pluses and minuses of possible settings to identify the optimal location for care. For example, individuals who require significant medical or surgical interventions or monitoring that are not typically available on a psychiatric inpatient service will likely be better served on a general hospital unit or intensive care setting with input from consultation-liaison psychiatrists. Considerable efforts may be needed to help staff who are unfamiliar with psychotic disorders to engage with the patient (Freudenreich et al. 2019). In other circumstances, management of the patient on an inpatient psychiatric service in collaboration with consultants of other medical specialties will be optimal.

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 and programs may include assertive community treatment (Substance Abuse and Mental Health Services Administration 2008), assisted outpatient treatment, intensive outpatient treatment, partial hospitalization, or day hospitalization.

Involuntary Treatment Considerations

Under some circumstances, individuals may not wish to participate in treatment or take medications, even if they have severe symptoms. In states where psychiatric advance directives are available, patients may be able to state their preferences about treatment choices while they have capacity in the event of future decompensation and an inability to participate in decision-making. Even in the absence of a psychiatric advance directive, patients can often be helped to accept pharmacological treatment over time and with psychotherapeutic interactions that are aimed toward identifying subjectively distressing symptoms that have previously responded to treatment. Family members and other persons of support can also be helpful in encouraging the patient to engage in treatment.

Prevailing state laws will determine other steps to take if an individual lacks capacity but requires treatment. Some states have processes by which pharmacological treatment may be administered involuntarily, whereas in other states a judicial hearing may be needed to obtain permission to treat a patient who lacks capacity.

For a small subgroup of patients with repeated relapses, re-hospitalizations, or even re-incarcerations associated with nonadherence or impairments in insight, involuntary outpatient commitment may warrant inclusion in the treatment plan to improve adherence, prevent psychiatric deterioration, enhance outcomes, and promote recovery (American Psychiatric Association 2015; Gaynes et al. 2015;

Harris et al. 2019; Segal et al. 2017a, 2017b; Swartz et al. 2017). Involuntary outpatient commitment (which also may be referred to as assisted outpatient treatment, mandated community treatment, outpatient court-ordered treatment, or a community treatment order) is increasingly available but varies among countries (Burns et al. 2013; Harris et al. 2019) and jurisdictions within the United States (Meldrum et al. 2016) in its criteria and implementation. Effective implementation requires adequate resources and individualized treatment planning (American Psychiatric Association 2015) if psychiatric (Gaynes et al. 2015; Harris et al. 2019; Segal et al. 2017a; Swartz et al. 2017) and physical health (Segal et al. 2017b) benefits are to be realized. As with any form of involuntary treatment, decisions about involuntary outpatient commitment require balancing ethical considerations related to patient autonomy and self-determination with considerations about the individual's best interest (American Psychiatric Association 2015).

Addressing Needs of Patients With Schizophrenia in Correctional Settings

Careful assessment and treatment planning are essential when individuals with schizophrenia are in correctional settings (e.g., prisons, jails, police lockups, detention facilities). Rates of serious mental illness, including schizophrenia, are higher in correctional settings than in the general population (Al-Rousan et al. 2017; Bebbington et al. 2017; Bradley-Engen 2010; Hall 2019; Steadman et al. 2009). Although some aspects of treatment may need to be adjusted to conform with unique aspects of correctional settings (Tamburello et al. 2018), many individuals experience gaps in care during incarceration (Fries et al. 2013; Reingle-Gonzalez et al. 2014; Wilper et al. 2009) and access should be preserved to essential elements of treatment, including antipsychotic medications (American Psychiatric Association 2009b) and treatment for concomitant substance use disorders (American Psychiatric Association 2007).

While in the correctional system, individuals with schizophrenia may be withdrawn, disorganized, or behave in a disruptive manner. These behaviors may result in disciplinary infractions, which may lead the individual with schizophrenia to be placed in a locked-down setting. Such units are often called "administrative segregation", "disciplinary segregation", or "restricted housing units" (Krelstein 2002; Semenza and Grosholz 2019) and have been conceptualized as having three main characteristics: social isolation, sensory deprivation, and confinement (Zubek et al. 1969). Each of these elements can vary significantly, but inmates typically spend an average of 23 hours per day in a cell, have limited human interaction and minimal or no access to programs, and are maintained in an environment that is designed to exert maximum control over the person, which has raised broader ethical considerations about the long-term use of such settings (Ahalt and Williams 2016; Ahalt et al. 2017; American Psychiatric Association 2017, 2018; American Public Health Association 2013; Cloud et al. 2015; National Commission on Correctional Health Care 2016).

Inmates' responses to the segregation experience differ, and relevant scientific literature is sparse (Kapoor and Trestman 2016; O'Keefe et al. 2013). In addition, mental health clinicians working in such facilities frequently report that inmates without preexisting serious mental disorders develop irritability, anxiety, and other dysphoric symptoms when housed in these units for long periods of time (Metzner 2002). Difficulties in providing appropriate and adequate access to mental health care and treatment are especially problematic in any segregation environment and are related to logistical issues that

frequently include inadequate office space and limited access to inmates because of security issues (Metzner 2003; Metzner and Fellner 2010). In addition, because of their inherently punitive structure, such units typically provide very little support, access to relevant treatment modalities, or a therapeutic milieu. Furthermore, rates of self-injury and suicide appear to be higher in such settings than elsewhere in the correctional system (Baillargeon et al. 2009b; Glowa-Kollisch et al. 2016; Kaba et al. 2014; Way et al. 2005). Consequently, persons with schizophrenia should generally not be placed in a 23-hour/day lockdown for behaviors that are directly related to schizophrenia, because such an intervention is likely to exacerbate rather than reduce psychotic symptoms, as well as increase rather than reduce disruptive behaviors (American College of Correctional Physicians 2013; American Psychiatric Association 2012, 2016b; American Public Health Association 2013; National Commission on Correctional Health Care 2016).

Individuals with schizophrenia, like other individuals with serious mental illness, are at increased risk for symptom relapse and gaps in treatment upon release from a correctional setting. Services are often needed to reduce the likelihood of recidivism and maintain continuity of care for treatment of schizophrenia and concomitant disorders (e.g., substance use disorders, other medical conditions). Thus, discharge planning is a crucial aspect of care for inmates with schizophrenia, particularly for those who have been incarcerated for significant periods of time. Often, inmates with schizophrenia have been alienated from systems of care and psychosocial supports prior to arrest, and this estrangement is compounded by incarceration. As a result, inmates will likely need assistance around the time of discharge, which can encompass various domains including housing, treatment needs, financial support and obtaining supplemental security income/social security disability and related Medicaid benefits (American Psychiatric Association 2009c; Angell et al. 2014; Baillargeon et al. 2009a, 2010; Draine et al. 2010; Gertner et al. 2019; Morrissey et al. 2016; Wenzlow et al. 2011).

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, 2017c; 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 document a comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments, and there is likely to be variability. Although a well-defined and scientifically-sound quality measure could be developed to assess for the implementation of an evidence-based treatment plan that meets consensus-based features of person-centered care, clinical judgment would still be needed to determine whether a documented treatment plan is comprehensive and adapted to individual needs and preferences. Manual review of charts to evaluate for the presence of such a person-centered treatment plan would be burdensome and time-consuming to implement.

A quality measure could assess the presence or absence of text in the medical record that would reflect treatment planning. When considering the development of such 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.

Pharmacotherapy

Statement 4: Antipsychotic Medications

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

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 with the patient the potential benefits and risks of medication as compared to other management options as part of selecting a medication. Many patients will wish family members or other persons of support to be involved in this discussion. 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 ranking of FGAs and 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. By the same token, it is not possible to note a preference for either SGAs or FGAs. 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, with the possible exception of clozapine. Although data in first episode schizophrenia is more limited, there appears to be no difference in response among the SGAs that have been studied (McDonagh et al. 2017; Zhu et al. 2017). 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 will typically occur in the context of discussion with the patient about the likely benefits and possible side effects of medication options and will incorporate patient preferences, the patient's past responses to 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.

(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.)

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Table 3. Antipsychotic medications: available oral and short-acting intramuscular formulations and dosing considerations^{1,2,3,4}

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
First-Generation Antipsychotics						

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

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. (Nuplazid (10 and 34 mg pimavanserin) 2018; Nuplazid (17 mg pimavanserin) 2018). 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.

³ Source. Hiemke et al. 2018; Koytchev et al. 1996; Lexicomp 2019; Micromedex 2019; Mountjoy et al. 1999; Procyshyn et al. 2019

⁴ Source. Package insert references: Abilify 2017, 2019; Abilify Maintena 2018; Abilify Mycite 2017; Aripiprazole orally disintegrating tablets 2018; Aripiprazole solution 2016; Aristada 2019; Aristada Initio 2019; Chlorpromazine hydrochloride injection 2010, 2016; Chlorpromazine hydrochloride tablets 2018; Clozapine 2017; Clozaril 2017, 2019; Fanapt 2017; FazaClo 2017; Fluphenazine decanoate injection 2018; Fluphenazine hydrochloride elixir 2016; Fluphenazine hydrochloride injection 2010; Fluphenazine hydrochloride solution, concentrate 2010; Fluphenazine hydrochloride tablets 2016; Geodon 2018; Haldol decanoate injection 2019; Haldol lactate injection 2019; Haloperidol 2008; Haloperidol lactate injection 2011; Haloperidol lactate oral solution 2016; Haloperidol tablets 2015; Invega 2018, 2019; Invega Sustenna 2018a, 2018b; Invega Trinza 2018a, 2018b; Latuda 2018; Loxapac 2014; Loxitane 2017; Moban 2017; Molindone hydrochloride tablets 2014, 2018; Navane 2010; Orap 2014, 2018, 2019; Perphenazine 2016, 2017; Perseris 2018; Rexulti 2019; Risperdal 2019; Risperdal Consta 2019; Risperidone orally disintegrating tablets 2019; Saphris 2017; Seroquel 2019; Seroquel XR 2019; Thioridazine hydrochloride 2016; Trifluoperazine 2017; Vraylar 2019; Zyprexa 2018a, 2018b; Zyprexa Relprevv 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.

⁹ As described in Pugh et al. 1973, Child-Pugh Class A corresponds to a Child-Pugh score of 5–6, class B corresponds to a Child-Pugh score of 7–9, and class C corresponds to the Child-Pugh Score of 10–15.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Chlorpromazine	Thorazine	Tablet: 10, 25, 50, 100, 200 Short-acting injection (HCl): 25/mL (1 mL, 2 mL)	25-100	200 – 800	Oral: 1000-2000	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.
Fluphenazine	Prolixin	Tablet: 1, 2.5, 5, 10 Oral Concentrate: 5/mL (120 mL) Elixir: 2.5/5 mL (60 mL) Short-acting injection (HCl): 2.5/mL (10 mL)	2.5 - 10	6 - 20	Oral: 40 IM: 10	Short-acting IM dose is 33-50% of oral dose. Dilute oral concentrate immediately before use to ensure palatability and stability.
Haloperidol	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)	1 - 15	5 - 20	Oral:100 IM: 20	2-5 mg IM can be given every 4-8 hours.
Loxapine	Loxitane	Capsule: 5, 10, 25, 50 Aerosol Powder Breath Activated Inhalation: 10	20	60 -100 ¹⁰	Oral: 250 Aerosol: 10	Oral inhalation formulation (Adasuve) to treat agitation requires REMS program due to potential for bronchospasm.
Molindone	Moban	Tablet: 5, 10, 25	50 - 75	30 – 100 ⁹	225	

¹⁰ Usually given in divided doses.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Perphenazine	Trilafon	Tablet: 2, 4, 8, 16	8 - 16	8 - 32	64	CYP2D6 poor metabolizers will have higher blood concentrations
Pimozide	Orap	Tablet: 1, 2	0.5 - 2	2 - 4	10	Does not have an FDA indication for schizophrenia but is sometimes used off-label or to treat delusional disorders such as delusional parasitosis. Avoid concomitant use of CYP1A2 or CYP3A4 inducers or inhibitors. 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.
Thioridazine	Mellaril	Tablet: 10, 25, 50, 100	150 - 300	300 – 800 ⁹	800	Use is associated with dose-related QTc prolongation. Baseline ECG and serum potassium level are recommended. Avoid use if QTc interval is > 450 msec or with concomitant use of drugs that prolong the QTc interval or inhibit CYP 2D6. Reserved use for patients who do not show an acceptable response to adequate courses of treatment with other antipsychotic drugs.
Thiothixene	Navane	Capsule: 1, 2, 5, 10	6 - 10	15-30	60	Smoking may reduce levels via CYP1A2 induction.
Trifluoperazine	Stelazine	Tablet: 1, 2, 5, 10	4 - 10	15-20	50	Smoking may reduce levels via CYP1A2 induction.
Second-Generation Antipsychotics						

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Aripiprazole	Abilify	Tablet: 2, 5, 10, 15, 20, 30 Tablet, Disintegrating: 10, 15 Tablet with Ingestible Event Marker (Mycite): 2, 5, 10, 15, 20, 30 Solution: 1/mL (150 mL)	10 -15	10-15	30	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 tablet cannot be split or crushed.
Asenapine	Saphris	Tablet, Sublingual: 2.5, 5, 10	10	20	20	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. Do not eat or drink for 10 minutes after administration to assure absorption.
Asenapine	Secuado	Transdermal system: 3.8 mg/24 hours, 5.7 mg/24 hours, 7.6 mg/24 hours	3.8	3.8-7.6	7.6	Consider dose adjustment in smokers and with concomitant use of CYP1A2 inhibitors. A dose of 3.8 mg/24 hours corresponds to 5 mg twice daily of sublingual asenapine; 7.6 mg/24 hours corresponds to 10 mg twice daily of sublingual asenapine. Apply to clean, dry, and intact skin on the upper arm, upper back, abdomen, or hip; rotate sites when applying a new transdermal system. Do not cut. Do not apply external heat sources to the transdermal system.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Brexpiprazole	Rexulti	Tablet: 0.25, 0.5, 1, 2, 3, 4	1	2 - 4	4	Adjust dose if a poor CYP2D6 metabolizer or with concomitant use of moderate/strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, or strong CYP3A4 inducers
Cariprazine	Vraylar	Capsule: 1.5, 3, 4.5, 6	1.5	1.5 - 6	6 ¹¹	Adjust dose with concomitant use of a strong CYP3A4 inhibitor or inducer.
Clozapine	Clozaril; FazaClo; Versacloz	Tablet: 25, 50, 100, 200 Tablet, Disintegrating: 12.5, 25, 100, 150, 200 Oral Suspension: 50/mL (100 mL)	12.5 – 25	300 - 450 ⁷	900	Prescribers must complete Clozapine REMS education (https://www.clozapinerems.com/) 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/day 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. With treatment interruptions of more than 30 days, recommendations for initial titration and monitoring frequency should be followed. 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. ¹²

¹¹ Up to 9 mg/d has been studied in clinical trials.

¹² 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.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Iloperidone	Fanapt	Tablet: 1, 2, 4, 6, 8, 10, 12	2	12-24	24	Titrate slowly (no more than 4 mg/day 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.
Lurasidone	Latuda	Tablet: 20, 40, 60, 80, 120	40	40-120	160	Administer with food (≥ 350 calories). Adjust dose for concomitant use of moderate to strong CYP3A4 inhibitors or inducers.
Olanzapine	Zyprexa	Tablet: 2.5, 5, 7.5, 10, 15, 20 Tablet, Disintegrating: 5, 10, 15, 20 Short-acting IM Powder for Solution: 10/2 mL	5-10	10-20	20 ¹³	Short-acting IM formulation 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 parenteral benzodiazepines is not recommended due to potential for excessive sedation and cardiorespiratory depression. Smokers may require a 30% greater daily dose than nonsmokers due to CYP1A2 induction. 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.

¹³ 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.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
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 5 days, up to a max of 12 mg/day. 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.
Quetiapine	Seroquel	Tablet, Immediate Release: 25, 50, 100, 200, 300, 400 Tablet, Extended Release: 50, 150, 200, 300, 400	Immediate Release: 50 Extended Release: 300	400-800	800	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 <300 calories. Re-titrate for gap in treatment of more than 1 week. Adjust dose for concomitant use of strong CYP3A4 inhibitors or inducers.

	Trade name ⁵	Available U.S. formulations (mg, unless otherwise noted)	Initial dose (mg/day)	Typical dose range (mg/day)	Maximum daily dose (mg/day)	Comments ^{6,7,8,9}
Risperidone	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)	2	2 - 8	8 ¹⁴	Lower initial doses and slower titration rates with CrCl <30 mL/min or severe hepatic impairment (Child-Pugh class C). Fraction of free risperidone is increased with hepatic impairment and the initial starting dose is 0.5 mg twice daily, which may be increased in increments of 0.5 mg or less, administered twice daily. With renal or hepatic impairment, increase in intervals of one week or greater for doses above 1.5 mg twice daily. Adjust dose with concomitant use of inducers or inhibitors of CYP2D6. Check labeling for compatible liquids with oral solution. Do not split or crush oral disintegrating tablets. Inform patients with phenylketonuria that oral disintegrating tablets contain phenylalanine.
Ziprasidone	Geodon	Capsule: 20, 40, 60, 80 Solution Reconstituted, IM: 20	40	80 – 160	320	Give capsules with >500 calories of food. No data suggests improved efficacy at higher doses. See labeling for reconstitution and storage of IM formulation. Short-acting IM formulation is used primarily for agitation with usual dose of 20 mg/day and max dose of 40 mg/day.

Abbreviations: ANC=absolute neutrophil count; CBC=complete blood count; CrCl=creatinine clearance; ECG=electrocardiography; FDA=Food and Drug Administration; HCl=hydrochloride; IM=intramuscular; IV=intravenous; OROS=osmotic-controlled release oral delivery system; QTc=corrected QT interval; REMS=risk evaluation and mitigation strategies

¹⁴ Doses of risperidone up to 16 mg/day have been studied in clinical trials; however, doses >6 mg for twice daily dosing do not appear to confer additional benefit and have a higher incidence of extrapyramidal symptoms than lower doses.

Table 4. Antipsychotic medications: pharmacokinetics/pharmacodynamics of oral and short-acting intramuscular formulations¹⁵

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
First-Generation Antipsychotics										
Chlorpromazine	Thorazine	32%	2.8 hours	90 - 99%	CYP2D6 (Major), CYP1A2 (Minor), CYP3A4 (Minor) substrate	NOR2CPZ, NOR2CPZ SULF, and 3-OH CPZ	Biphasic: initial 2 hours, terminal 30 hours	Primarily renal (<1% as unchanged drug)	Use with caution	Use with caution; not dialyzable
Fluphenazine	Prolixin	2.7%	Oral: 2 hours IM: 1.5 – 2 hours	99%	CYP2D6 (Major) substrate	7-hydroxyfluphenazine, fluphenazine-sulfoxide	4.4 to 16.4 hours	Renal and fecal; exact proportion unclear	Contraindicated by manufacturer	Use with caution
Haloperidol	Haldol	60-70%	Oral: 2-6 hours IM: 20 min	89-93%	CYP2D6 (Major), CYP3A4 (Major), CYP1A2 (Minor) substrate; 50-60% glucuronidation	Hydroxymetabolite-reduced haloperidol	14 to 37 hours	15% fecal; 30% renal (1% as unchanged drug); + enterohepatic circulation	No dose adjustments noted	No dose adjustments noted

¹⁵ 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

¹⁶ As described in Pugh et al. 1973, Child-Pugh Class A corresponds to a Child-Pugh score of 5–6, class B corresponds to a Child-Pugh score of 7–9, and class C corresponds to the Child-Pugh Score of 10–15.

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Loxapine	Loxitane	99%	1.5 - 3 hours	97%	CYP1A2 (Minor), CYP2D6 (Minor), CYP3A4 (Minor) substrate; P-glycoprotein inhibitor	N-desmethyl loxapine (amoxapine), 8-hydroxyloxapine	Biphasic: initial 5 hours, terminal 19 hours	Renal and fecal	No dose adjustments noted	No dose adjustments noted
Molindone	Moban	Unclear	1.5 hours	76%	CYP2D6	Multiple	1.5 hours	Renal and fecal	Use with caution	No dose adjustments noted
Perphenazine	Trilafon	20 - 40%	Perphenazine: 1 - 3 hours, 7-hydroxyperphenazine: 2 - 4 hours	91-99%	CYP2D6 (Major) substrate, CYP1A2 (Minor), CYP2C19 (Minor), CYP2C9 (Minor), CYP3A4 (Minor) substrate	7-hydroxyperphenazine (responsible for 70% of the activity)	Perphenazine: 9-12 hours 7-hydroxyperphenazine: 10-19 hours	5% fecal; 70% renal	Contraindicated in liver damage	Use with caution
Pimozide	Orap	≥50%	6 - 8 hours	99%	CYP1A2 (Major), CYP2D6 (Major), CYP3A4 (Major) substrate	Unknown activity: 4-bis-(4-fluorophenyl) butyric acid, 1-(4-piperidyl)-2-benzimidazolinone	55 hours	Primarily renal	Use with caution	Use with caution
Thioridazine	Mellaril	25-33%	1 - 4 hours	96-99%	CYP2D6 (Major) substrate and moderate inhibitor, CYP2C19 (Minor) substrate	Mesoridazine (twice as potent as thioridazine), sulphoridazine	21-24 hours	Minimal renal	Use with caution	No dose adjustments noted

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Thiothixene	Navane	~50%; erratic absorption	1 - 2 hours	90%	CYP1A2 (Major) substrate	None noted	34 hours	Feces (unchanged drug and metabolites)	No dose adjustments noted	No dose adjustments noted
Trifluoperazine	Stelazine	Erratic absorption	1.5 - 6 hours	90-99%	CYP1A2 (Major) substrate	N-desmethyltrifluoperazine, 7-hydroxytrifluoperazine, and other metabolites	3 - 12 hours	Renal	Contraindicated in hepatic disease	No dose adjustments noted
Second-Generation Antipsychotics										
Aripiprazole	Abilify	87%	3 - 5 hours	>99%	CYP2D6 (Major), CYP3A4 (Major) substrate	Dehydro-aripiprazole	75 hours; 94 hours dehydro-aripiprazole 146 hours in poor CYP2D6 metabolizers	55% fecal 25% renal	No dose adjustments noted	No dose adjustments noted

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Asenapine	Saphris	35%	0.5 - 1.5 hours	95%	CYP1A2 (Major), CYP2D6 (Minor), CYP3A4 (Minor) substrate; glucuronidation by UGT1A4; CYP2D6 weak inhibitor	Inactive: N(+)-glucuronide, N-desmethyiasenapine, and N-desmethyiasenapine N-carbamoyl glucuronide	24 hours	40% fecal 50% renal	Use is contraindicated in severe hepatic impairment (Child-Pugh class C)	No dose adjustments noted
Asenapine	Secuado	N/A	--	95%	CYP1A2 (Major), CYP2D6 (Minor), CYP3A4 (Minor) substrate; glucuronidation by UGT1A4; CYP2D6 weak inhibitor	Inactive: N(+)-glucuronide, N-desmethyiasenapine, and N-desmethyiasenapine N-carbamoyl glucuronide	24 hours	40% fecal 50% renal	Use is contraindicated in severe hepatic impairment (Child-Pugh class C)	No dose adjustments noted
Brexiprazole	Rexulti	95%	4 hours	>99%	CYP3A4 (Major), CYP2D6 (Major) substrate	Inactive: DM-3411	91 hours	46% fecal 25% renal	Moderate - severe impairment (Child-Pugh class B or C): use maximum dose of 2 mg/day in: MDD and: 3 mg/day in schizophrenia	CrCl <60 mL/min: use maximum dose of 2 mg/day in: MDD and: 3 mg/day in schizophrenia

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Cariprazine	Vraylar	High	3-6 hours	91-97%	CYP3A4 (Major), CYP2D6 (Minor) substrate	Desmethyl cariprazine [DCAR], didesmethyl cariprazine [DDCAR]	Cariprazine 2 - 4 days DCAR: 1-2 days DDCAR: 1-3 weeks	21% renal	Severe impairment (Child-Pugh class C): not recommended	CrCl <30 mL/min: not recommended
Clozapine	Clozaril; FazaClo; Versacloz	27 - 60%	2.2 - 2.5 hours (range: 1-6 hours)	97%	CYP1A2 (Major), CYP2A6 (Minor), CYP2C19 (Minor), CYP2C9 (Minor), CYP2D6 (Minor), CYP3A4 (Minor) substrate	N-desmethylozapine (active), hydroxylated and n-oxide derivatives (inactive)	4 – 66 hours (steady state 12 hours)	30% fecal 50% renal	Significant impairment: dose reduction may be necessary	Significant impairment: dose reduction may be necessary

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Iloperidone	Fanapt	96%	2 - 4 hours	92-97%	CYP2D6 (Major), CYP3A4 (Minor) substrate, CYP3A4 weak inhibitor	P88 P95	Extensive metabolizers : Iloperidone 18 hours, P88 26 hours, P95 23 hours Poor metabolizers : iloperidone 33 hours, P88 37 hours, P95 31 hours	~20% fecal ~50% renal	Moderate impairment: use with caution Severe impairment: not recommended	No dose adjustments noted
Lurasidone	Latuda	9-19%	1-3 hours	99%	CYP3A4 (Major) substrate, CYP3A4 weak inhibitor	ID-14283, ID-14326 (active); ID20219, ID-20220 (inactive)	Lurasidone 18-40 hours; ID-14283: 7.5-10 hours	~80% fecal ~9% renal	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	For CrCl < 50 mL/min: initial 20 mg/day, maximum dose is 80 mg/day

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Olanzapine	Zyprexa	>57%	Oral: 6 hours IM: 15-45 mins	93%	CYP1A2 (Major), CYP2D6 (Minor) substrate; metabolized via direct glucuronidation	10-N-glucuronide, 4-N-desmethyl olanzapine (inactive)	30 hours	30% fecal 57% renal	Use with caution	Not removed by dialysis
Paliperidone	Invega	28%	24 hours	74%	P-glycoprotein/ABCB1, CYP2D6(Minor), CYP3A4 (Minor) substrate	Activity unclear: M1, M9, M10, M11, M12, M16	23 hours; 24-51 hours with renal impairment (CrCl <80ml/min)	11% fecal 80% renal	Mild – moderate: no adjustment necessary Severe: not studied	Not recommended for CrCl < 10 mL/min. CrCl 10 - 49 mL/min and for CrCl of 50 - 79 mL/min, use max dose of 3 mg/day and 6 mg/day, respectively.

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Quetiapine	Seroquel	100%	Immediate release: 1.5 hours; Extended release: 6 hours	83%	CYP3A4 (Major), CYP2D6 (Minor) substrate	Active: Norquetiapine, 7-hydroxyquetiapine Inactive: quetiapine sulfoxide (Major), parent acid metabolite	Quetiapine: 6 - 7 hours Norquetiapine: 12 hours	20% fecal 73% renal	Immediate release: initial 25 mg/day dose, increase by 25 - 50 mg/day to effective dose Extended release: initial 50 mg/d, increase by 50 mg/day to effective dose	No dose adjustments noted

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Risperidone	Risperdal	Absolute: 70% Tablet relative to oral solution: 94%	1 hour	90%	CYP2D6 (Major), CYP3A4 (Minor), P-glycoprotein/ABCB1 substrate, N-dealkylation (minor), CYP2D6 weak inhibitor	Active: 9-hydroxy-risperidone	Risperidone 3 - 20 hours 9-hydroxy-risperidone 21 - 30 hours	14% fecal 70% renal	Mild or moderate impairment (Child-Pugh class A or B): reduce dose 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 > 1.5 mg twice a day at 1 week or greater	Mild or moderate impairment (CrCl \geq 30 mL/min): reduce dose Severe impairment (CrCl <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 > 1.5 mg twice a day at 1 week or greater

	Trade name	Oral bioavailability	Time to peak level	Protein binding	Metabolic enzymes/transporters	Metabolites	Elimination half-life in adults	Excretion	Hepatic impairment ¹⁶	Renal impairment
Ziprasidone	Geodon	Oral with food: 60%; IM:100%	Oral: 6 - 8 hours IM: 60 mins	>99%	CYP1A2 (Minor), CYP3A4 (Minor) substrate, glutathione, aldehyde oxidase	Active: benisothiazole sulphoxide (Major), benisothiazole sulphone (Major), ziprasidone sulphoxide, s-methyl-dihydroziprasidone	Oral: 7 hours; IM: 2 - 5 hours	66% fecal 20% renal	Use with caution	No oral dose adjustments noted; IM formulation contains a renally cleared excipient, cyclodextrin - use with caution.

Abbreviations: CrCl=creatinine clearance; IM=intramuscular; MDD=major depressive disorder

Table 5. Antipsychotic receptor binding properties¹⁷

	Trade name	D1	D2	D3	D4	D5	5HT-1A	5HT-2A	5HT-2C	5HT-7	H1	Musc M1	Alpha 1	Alpha 2	Comments
First-Generation Antipsychotics															
Chlorpromazine	Thorazine	+	+++	+++	++	+	0	+++	++	++	+++	++	+++	+	
Fluphenazine	Prolixin	++	++++	++++	++	++	+	++	+	+++	++	0	+++	0	
Haloperidol	Haldol	+	+++	+++	+++	+	0	++	0	+	0	0	++	0	

¹⁷ Source. Abilify 2018; Latuda 2018; Lexicomp 2019; Maeda et al. 2014; Micromedex 2019; Olten and Bloch 2018; PDSP Ki database 2019; Procyshyn et al. 2019; Roth et al. 2000; Saphris 2017; Vraylar 2019

	Trade name	D1	D2	D3	D4	D5	5HT-1A	5HT-2A	5HT-2C	5HT-7	H1	Musc M1	Alpha 1	Alpha 2	Comments
Loxapine	Loxitane	++	++	++	+++	++	0	+++	++	++	+++	+	++	0	
Molindone	Moban	0	++	++	0		0	0	0	0	0	0	0	+	
Perphenazine	Trilafon	++	++++	++++	++		0	+++	+	++	+++	0	++	+	
Pimozide	Orap	0	++++	+++	++		+	++	0	++++	+	+	+	+	Moderate activity at dopamine transporter
Thioridazine	Mellaril	++	++	+++	++	+	+	++	++	++	++	+++	+++	+	
Thiothixene	Navane	+	++++	++++	+	+	+	++	0	++	+++	0	++	0	
Trifluoperazine	Stelazine	+	+++	++++	++		+	++	+	+	++	+	++	0	
Second-Generation Antipsychotics															
Aripiprazole	Abilify	+	///	+++	+	0	///	+++	++	++	++	0	++	+	
Asenapine	Saphris, Secuado	+++	+++	++++	+++		+++	++++	++++	++++	+++	0	+++	+++	
Brexpiprazole	Rexulti	+	///	+++	++++		///	++++	++	+++	++	0	+++	++++	
Cariprazine	Vraylar		///	++++			///	++	+	+	++	0	+		
Clozapine	Clozaril; FazaClo; Versacloz	+	+	+	++	+	/	+++	++	++	+++	///	+++	+	
Iloperidone	Fanapt	+	++	++	++	+	//	++++	++	++	+	0	+++	+++	

	Trade name	D1	D2	D3	D4	D5	5HT-1A	5HT-2A	5HT-2C	5HT-7	H1	Musc M1	Alpha 1	Alpha 2	Comments
Lurasidone	Latuda	+	+++	++	++		/	++++	+	++++	0	0	++	++	
Olanzapine	Zyprexa	++	++	++	++	++	0	+++	++	+	+++	+++	++	+	
Paliperidone	Invega	+	+++	+++	++	++	+	++++	++	+++	+++	0	+++	++	
Quetiapine	Seroquel	0	+	+	0	0	/	+	0	+	+++	+	++	0	
Risperidone	Risperdal	+	+++	+++	+++	+	+	++++	++	+++	++	0	+++	+++	
Ziprasidone	Geodon	+	+++	+++	++	+	///	++++	++++	+++	++	0	+++	+	Weak activity at norepinephrine and serotonin transporter

Note: ++++ = very strong binding ($K_i < 1$ nM); +++ = strong binding (1 nM $\leq K_i < 10$ nM); ++ = moderate binding (10 nM $\leq K_i < 100$ nM); + = weak binding (100 nM $\leq K_i < 1000$ nM); 0 = very weak or negligible binding ($K_i \geq 1000$ nM). For partial agonists, / is used to denote relative binding values instead of +.

Table 6. Antipsychotic medications: relative side effects of oral formulations¹⁸

	Trade name	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyperprolactinemia ¹⁹	Anticholinergic	Sedation
First-Generation Antipsychotics								
Chlorpromazine	Thorazine	++	++	++	+++	+	+++	+++
Fluphenazine	Prolixin	+++	+++	+++	+++	+++	+	+

¹⁸ Source. Credible Meds 2019; Hirsch et al. 2017; La Torre et al. 2013; Lexicomp 2019; Micromedex 2019; Pisani et al. 2002; Procyshyn et al. 2019; van Dijk et al. 2018

¹⁹ In general, rates of sexual dysfunction parallel rates of hyperprolactinemia except where noted in comments.

	Trade name	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyper-prolactinemia ¹⁹	Anticholinergic	Sedation
Haloperidol	Haldol	+++	+++	+++	+++	+++	+	+
Loxapine	Loxitane	++	++	++	++	++	++	++
Molindone	Moban	++	++	++	++	++	+	++
Perphenazine	Trilafon	++	++	++	++	++	++	++
Pimozide	Orap	+++	+++	++	+++	+++	+	+
Thioridazine	Mellaril	+	+	+	+	++	+++	+++
Thiothixene	Navane	+++	+++	+++	+++	+++	+	+
Trifluoperazine	Stelazine	++	++	++	++	++	++	+
Second-Generation Antipsychotics								
Aripiprazole	Abilify	++	+	+	+	+	+	+
Asenapine	Saphris	++	+	++	++	++	+	++
Brexpiprazole	Rexulti	++	+	+	+	+	+	++
Cariprazine	Vraylar	++	+	+	+	+	++	++
Clozapine	Clozaril; FazaClo; Versacloz	+	+	+	+	+	+++	+++
Iloperidone	Fanapt	+	+	+	+	++	+	++
Lurasidone	Latuda	++	++	++	++	+	+	++
Olanzapine	Zyprexa	++	++	+	+	++	++	+++

	Trade name	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyper-prolactinemia ¹⁹	Anticholinergic	Sedation
Paliperidone	Invega	++	++	++	++	+++	+	+
Quetiapine	Seroquel	+	+	+	+	+	++	+++
Risperidone	Risperdal	++	++	++	++	+++	+	++
Ziprasidone	Geodon	++	+	+	+	++	+	++

Table 6. Antipsychotic medications: relative side effects of oral formulations (continued)

	Trade name	Seizures	Orthostasis	QT prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities	Comments
First-Generation Antipsychotics								
Chlorpromazine	Thorazine	++	+++	+++	++	+	++	
Fluphenazine	Prolixin	+	+	++	++	+	+	
Haloperidol	Haldol	+	+	++	++	+	+	
Loxapine	Loxitane	+	++	++	+	+	+	
Molindone	Moban	+	+	++	+	+	+	
Perphenazine	Trilafon	+	++	++	++	+	+	
Pimozide	Orap	+++	+	+++	+	+	+	
Thioridazine	Mellaril	++	+++	+++	++	+	+	Pigmentary retinopathy; high rates of sexual dysfunction; avoid use if QTc interval is > 450 msec or with

	Trade name	Seizures	Orthostasis	QT prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities	Comments
								concomitant use of drugs that prolong the QTc interval or inhibit CYP 2D6.
Thiothixene	Navane	+++	+	++	+	+	+	
Trifluoperazine	Stelazine	+	+	++	++	+	+	
Second-Generation Antipsychotics								
Aripiprazole	Abilify	+	+	+	+	+	+	FDA safety alert for impulse control disorders (e.g., gambling, binge eating); may reduce hyperprolactinemia with other antipsychotics
Asenapine	Saphris	+	++	++	++	++	++	Oral hypoesthesia
Brexpiprazole	Rexulti	+	+	++	+	++	+	
Cariprazine	Vraylar	+	+	++	++	+	+	
Clozapine	Clozaril; FazaClo; Versacloz	+++	+++	++	+++	+++	+++	Increased salivation common; high rate of sexual dysfunction; severe constipation and paralytic ileus possible; fever can occur with initiation; myocarditis is infrequent; cardiomyopathy and severe neutropenia are rare.
Iloperidone	Fanapt	+	+++	+++	++	+	++	
Lurasidone	Latuda	+	+	+	+	++	++	Dose-related creatinine increase in some patients
Olanzapine	Zyprexa	++	++	++	+++	+++	+++	

	Trade name	Seizures	Orthostasis	QT prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities	Comments
Paliperidone	Invega	+	++	++	++	++	+	
Quetiapine	Seroquel	++	++	++	++	+++	++	
Risperidone	Risperdal	+	++	++	++	+	++	Intraoperative floppy iris syndrome reported
Ziprasidone	Geodon	+	++	+++	+	+	+	

Table 7. Long-acting injectable antipsychotic medications: availability and injection related considerations^{20,21}

	Trade name	Available strengths ²² (mg, unless otherwise noted)	How supplied	Injection site and technique ²³	Reactions at injection site ²⁴	Comments
First-Generation Antipsychotics						

²⁰ 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.

²¹ *Source.* Abilify 2018; Aristada 2019; Aristada Initio 2019; Andorn et al. 2019; Invega Sustenna 2018; Invega Trinza 2018; ; Lexicomp 2019; Micromedex 2019; Perseris 2018; Procyshyn et al. 2019; Risperdal Consta 2019; Zyprexa Relprev 2018

²² Available strengths are based on U.S. products; strengths and products available in other countries may differ.

²³ Each injection must be administered only by a healthcare professional. Long-acting injectable antipsychotic medications should never be administered intravenously.

²⁴ Pain at injection site noted for all products.

	Trade name	Available strengths ²² (mg, unless otherwise noted)	How supplied	Injection site and technique ²³	Reactions at injection site ²⁴	Comments
Fluphenazine	Prolixin Decanoate	25/mL (5 mL)	Vial, Sesame oil vehicle with 1.2% benzyl alcohol	Deep IM gluteal or deltoid injection, use of Z-track technique recommended ²⁵	Skin reactions reported	Monitor for hypotension. In sesame oil; be alert for allergy. For detailed instructions on needle size and product handling, refer to labelling.
Haloperidol	Haldol Decanoate	50/mL (1 mL, 5 mL), 100/mL (1 mL, 5 mL)	Vial, Sesame oil vehicle with 1.2% benzyl alcohol	Deep IM gluteal or deltoid injection; use of Z-track technique recommended	Inflammation and nodules reported, especially with dose > 100 mg/ml	Do not administer more than 3 mL per injection site. In sesame oil; be alert for allergy. For detailed instructions on needle size, refer to labelling.
Second-Generation Antipsychotics						
Aripiprazole monohydrate	Abilify Maintena	300, 400	Kit with either pre-filled syringe or single use vial	Slow IM injection into gluteal or deltoid muscle	Occasional redness, swelling, induration (mild to moderate)	Rotate injection sites; do not massage muscle after injection. For detailed instructions on needle size and product reconstitution, refer to labelling.
Aripiprazole lauroxil	Aristada Initio	675/2.4 mL	Kit with pre-filled syringe	IM deltoid or gluteal muscle	Common: pain; Infrequent: induration, swelling, redness	Only to be used as a single dose to initiate Aristada treatment or to re-initiate treatment following a missed dose of Aristada. Not for repeat dosing. Not interchangeable with Aristada. Avoid concomitant injection of Aristada Initio and Aristada into the same deltoid or gluteal muscle. Refer to labelling for detailed instructions on injection site, needle length, and instructions to ensure a uniform suspension.

²⁵ Source. Government of South Australia Health: Injection Sites. Available at: www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/medicines+and+drugs/injection+techniques#Z%20track. Accessed January 20, 2019.

Northumberland, Tyne and Wear NHS Foundation Trust: Standard for the Assessment and Management of Physical Health. Appendix 2 Injection Sites. Available at: www.ntw.nhs.uk/content/uploads/2015/06/AMPH-PGN-10-IMI-App2-Injection-Sites-V01-iss-Sep7.pdf. Accessed January 20, 2019.

	Trade name	Available strengths ²² (mg, unless otherwise noted)	How supplied	Injection site and technique ²³	Reactions at injection site ²⁴	Comments
Aripiprazole lauroxil	Aristada	441/1.6 mL 662/2.4 mL 882 /3.2 mL 1064/3.9 mL	Kit with pre-filled syringe	IM deltoid or gluteal muscle for 441 mg IM gluteal muscle for 662 mg, 882 mg, or 1064 mg	Common: pain; Infrequent: induration, swelling, redness	Not interchangeable with Aristada Initio. Avoid concomitant injection of Aristada Initio and Aristada into the same deltoid or gluteal muscle. Refer to labelling for detailed instructions on injection site, needle length, and instructions to ensure a uniform suspension.
Olanzapine	Zyprexa Relprevv	210, 300, 405	Kit with vial containing diluent and vial with powder for reconstituting suspension	Deep IM gluteal injection only; do not administer subcutaneously	Infrequent induration or mass at injection site	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 (www.zyprexa-relprevv-program.com/public/Default.aspx). Do not massage muscle after injection. The combined effects of age, smoking, and gender may lead to significant pharmacokinetic differences. For detailed instructions on product handling and reconstitution, refer to labelling.
Paliperidone palmitate	Invega Sustenna	39/0.25 mL, 78/0.5 mL, 117/0.75 mL, 156/mL, 234/1.5 mL	Kit with pre-filled syringe	IM only; Slow deep IM deltoid injection for first 2 doses, then deep deltoid or gluteal injection (upper outer quadrant) thereafter	Occasional redness, swelling, induration	The two initial deltoid IM injections help attain therapeutic concentrations rapidly. Alternate deltoid injections (right and left deltoid muscle). For detailed instructions on needle size and product reconstitution, refer to labelling.

	Trade name	Available strengths ²² (mg, unless otherwise noted)	How supplied	Injection site and technique ²³	Reactions at injection site ²⁴	Comments
Paliperidone palmitate	Invega Trinza	273/0.875 mL, 410/1.315 mL, 546/1.75 mL, 819/2.625 mL	Kit with pre-filled syringe	IM only; Slow deep IM deltoid or gluteal injection	Infrequent redness or swelling	Shake prefilled syringe for 15 seconds within 5 minutes prior to administration. For detailed instructions on needle size, product handling, and reconstitution, refer to labelling.
Risperidone	Risperdal Consta	12.5, 25, 37.5, 50	Kit with pre-filled syringe and vial for reconstitution	Deep IM injection into the deltoid or gluteal (upper outer quadrant)	Occasional redness, swelling, induration	Alternate injection sites. Refrigerate and store at 2°C to 8°C and protect from light. Vial should come to room temperature for at least 30 minutes before reconstituting. May be stored at 25°C for up to 7 days prior to administration. For detailed instructions on product handling and reconstitution, refer to labelling.
Risperidone	Perseris	90/0.6 mL, 120/0.8 mL	Kit with pre-filled syringes containing powder and diluent.	Abdominal subcutaneous injection only	Lump at injection site may persist for several weeks	Alternate injection sites. Inject only in area without skin conditions, irritation, reddening, bruising, infection, or scarring; do not rub or massage injection sites. Store at 2°C to 8°C and protect from light. Allow package to come to room temperature for at least 15 mins before injection. For detailed instructions on product handling and reconstitution, refer to labelling.

Abbreviations: FDA=Food and Drug Administration; IM=intramuscular; REMS=risk evaluation and mitigation strategies

Table 8. Long-acting injectable antipsychotic medications: dosing²⁶

²⁶ Source. Abilify 2018; Aristada 2019; Aristada Initio 2019; Bai et al. 2007; Hamann et al. 1990; Invega Sustenna 2018; Invega Trinza 2018; Kreyenbuhl et al. 2010; Lexicomp 2019; Micromedex 2019; Nasser et al. 2016; Perseris 2018; Procyshyn et al. 2019; Risperdal Consta 2019; Zyprexa Relprev 2018

	Trade name	Dose conversions	Initial dose (mg)	Typical dose (mg)	Maximum dose (mg)	Dosing frequency	Need for initial oral supplementation	Comments
First-Generation Antipsychotics								
Fluphenazine	Prolixin Decanoate	For each 10 mg/day oral, give 12.5 mg decanoate every 3 weeks	6.25 - 25 every 2 weeks	6.25 – 25 every 2-4 weeks	100	2-4 weeks	Decrease oral dose by half after first injection then discontinue with second injection	Increase in 12.5 mg increments if doses over 50 mg are needed
Haloperidol	Haldol Decanoate	For each 5 mg/day oral, give 50-75 mg decanoate every 4 weeks	Determined by oral dose and/or risk of relapse up to a maximum of 100 mg	50-200 (10-15 times previous oral dose)	450/month	4 weeks	Taper and discontinue after 2 to 3 injections	If initial dose is more than 100 mg, split into 2 injections separated by 3 to 7 days.
Second-Generation Antipsychotics								
Aripiprazole	Abilify Maintena	Not applicable	400	400	400/month	Monthly	Continue oral for 14 days after initial injection	Follow labeling if scheduled injections are missed; dose adjust for poor CYP2D6 metabolizers, those on CYP2D6 and/or CYP3A4 inhibitors, or due to adverse effects. Avoid use with CYP3A4 inducers.

	Trade name	Dose conversions	Initial dose (mg)	Typical dose (mg)	Maximum dose (mg)	Dosing frequency	Need for initial oral supplementation	Comments
Aripiprazole lauroxil	Aristada Initio	Not applicable	675	675	675	Single dose to initiate Aristada treatment or re-initiate treatment after a missed Aristada dose. Not for repeated dosing.	Must be administered in conjunction with one 30 mg dose of oral aripiprazole.	For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole before use. Aristada Initio and Aristada are not interchangeable. See labelling for dose adjustments.
Aripiprazole lauroxil	Aristada	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	Monthly: 441, 662, 882 Every 6 weeks: 882 Every 2 months: 1064	Monthly: 441, 662, 882 Every 6 weeks: 882 Every 2 months: 1064	882/month	Monthly: 441, 662, 882 Every 6 weeks: 882 Every 2 months: 1064	There are 2 ways to initiate treatment: 1. Give one IM injection of Aristada Initio 675 mg and one dose of oral aripiprazole 30 mg OR 2. Give 21 days of oral aripiprazole in conjunction with the first Aristada injection	Aristada Initio and Aristada are not interchangeable. The first Aristada injection may be given on the same day as Aristada Initio or up to 10 days thereafter.

	Trade name	Dose conversions	Initial dose (mg)	Typical dose (mg)	Maximum dose (mg)	Dosing frequency	Need for initial oral supplementation	Comments
Olanzapine	Zyprexa Relprevv	10 mg/day orally, 210 mg every 2 weeks for 4 doses or 405 mg every 4 weeks 15 mg/day orally, 300 mg every 2 weeks for 4 doses 20 mg/day orally, 300 mg every 2 weeks	Determined by oral dose	150 mg, 210 mg or 300 mg every 2 weeks, or 300 mg or 405 mg every 4 weeks	300 mg every 2 weeks or 405 mg every 4 weeks	2-4 weeks	Not required	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.
Paliperidone palmitate	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	234 mg IM on day 1 and 156 mg IM 1 week later both administered in the deltoid muscle	78 to 234 mg monthly beginning at week 5	234 mg/month	Monthly	Not required	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.

	Trade name	Dose conversions	Initial dose (mg)	Typical dose (mg)	Maximum dose (mg)	Dosing frequency	Need for initial oral supplementation	Comments
Paliperidone palmitate	Invega Trinza	Conversion from monthly Invega Sustenna to every 3-month injections of Invega Trinza. 78mg give 273 mg 117 mg give 410 mg 156 mg give 546 mg 234 mg give 819 mg	Dependent upon last dose of monthly paliperidone	273 - 819	819/3 months	Every 3 months	Not applicable	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.
Risperidone	Risperdal Consta	Oral risperidone to Risperidone Consta IM: ≤3 mg/day, give 25 mg/2 weeks > 3 to ≤ 5 mg/day, give 37.5 mg/2 weeks > 5 mg/day, give 50 mg/2 weeks	25 every 2 weeks	25 - 50 every 2 weeks	50 every 2 weeks	2 weeks	Continue oral for 3 weeks (21 days)	Upward dose adjustment should not be made more frequently than every 4 weeks.

	Trade name	Dose conversions	Initial dose (mg)	Typical dose (mg)	Maximum dose (mg)	Dosing frequency	Need for initial oral supplementation	Comments
Risperidone	Perseris	Oral risperidone to subcutaneous risperidone extended release: 3 mg/day, give 90 mg/monthly 4 mg/day, give 120 mg/monthly	Determined by oral dose	90 - 120 monthly	120/month	Monthly	Neither a loading dose nor oral overlap is needed	May not be appropriate for patients on less than 3 mg or more than 4 mg of oral risperidone daily. Adjust dose with concomitant CYP2D6 inhibitors or CYP3A4 inducers.

Abbreviations: IM=intramuscular; LAI=long-acting injectable

Table 9. Long-acting injectable antipsychotic medications: pharmacological characteristics²⁷

	Trade name	Time to peak plasma level	Time to steady state	Elimination half-life	Comments ²⁸
First-Generation Antipsychotics					
Fluphenazine	Prolixin Decanoate	8-10 hours	2 months	6-9 days for single injection and 14-26 days for multiple doses	Major CYP2D6 substrate
Haloperidol	Haldol Decanoate	6 days	3-4 months	21 days	Major CYP2D6 and CYP3A4 substrate
Second-Generation Antipsychotics					

²⁷ Source. Abilify 2018; Aristada 2019; Aristada Initio 2019; Invega Sustenna 2018; Invega Trinza 2018; Jann et al. 1985; Lexicomp 2019; Lindenmayer 2010; Micromedex 2019; Perseris 2018; Procyshyn et al. 2019; Risperdal Consta 2019; Saklad 2018; Zyprexa Relprevv 2018

²⁸ 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.

	Trade name	Time to peak plasma level	Time to steady state	Elimination half-life	Comments ²⁸
Aripiprazole	Abilify Maintena	4 days (deltoid); 5 - 7 days (gluteal)	By 4 th dose	300 mg: 29.9 days, 400 mg: 46.5 days (400 mg) with gluteal injection	Give no sooner than 26 days between injections Major CYP2D6 and CYP3A4 substrate
Aripiprazole lauroxil	Aristada Initio	16 - 35 days (median 27 days)	Not applicable	15 to 18 days	Not interchangeable with Aristada due to differing pharmacokinetic profiles. CYP2D6 and CYP3A4 substrate
Aripiprazole lauroxil	Aristada	Not available	4 months	53.9 to 57.2 days	Not interchangeable with Aristada Initio due to differing pharmacokinetic profiles. CYP2D6 and CYP3A4 substrate
Olanzapine	Zyprexa Relprevv	7 days	~3 months	30 days	Major CYP1A2 substrate
Paliperidone palmitate	Invega Sustenna	13 days	2-3 months	25 - 49 days; increased in renal disease	CrCl 50 - 79 mL/min: initiate at 156 mg on day 1, followed by 117 mg 1 week later, both administered in the deltoid muscle. Maintenance dose of 78 mg; Use not recommended in patients with CrCl < 50 mL/min Substrate of P-glycoprotein/ABCB1
Paliperidone palmitate	Invega Trinza	30 - 33 days	Not applicable	84 - 95 days with deltoid injection; 118 - 139 days with gluteal injection; increased in renal disease	Do not use in patients with CrCl <50 mL/min. Substrate of P-glycoprotein/ABCB1
Risperidone	Risperdal Consta	29 - 31 days	2 months	3 - 6 days; increased in renal or hepatic disease	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

	Trade name	Time to peak plasma level	Time to steady state	Elimination half-life	Comments ²⁸
					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
Risperidone	Perseris	Two peaks: 4 - 6 hours and 10 - 14 days	2 months	9 - 11 days	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

Abbreviations: CrCl=creatinine clearance; IM=intramuscular

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 ingestion, although the U.S. FDA notes that improvements in adherence have not yet been shown (U.S. 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 may be particularly useful for patients with a history of poor or uncertain adherence. (See Statement 10.) 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 interactions at metabolic enzymes such as cytochrome P450 (CYP) enzymes, UDP-glucuronosyltransferases, and flavin-containing monooxygenases (Ouzzine et al. 2014; Phillips and Shephard 2017; Rowland et al. 2013; Zanger and Schwab 2013). In particular, hepatic metabolism of antipsychotic medications via CYP enzymes has been widely studied (Lexicomp 2019; Micromedex 2019). 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., Δ^9 -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 (Eum et al. 2016; 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 (Bousman and Dunlop 2018; Koopmans et al. 2018; Lagishetty et al. 2016), 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) (U.S. Food and Drug Administration 2011). In addition, product labeling for a number of other antipsychotic medications refers to a need for dose adjustments based on metabolizer status (U.S. Food and Drug Administration 2019). Additional information on the clinical pharmacogenomics of antipsychotic medications is available through the Clinical Pharmacogenetics Implementation Consortium (<https://cpicpgx.org/>; Relling and Klein 2011), the Pharmacogene Variation Consortium (www.pharmvar.org/; Gaedigk et al. 2018), and the Pharmacogenomics Knowledgebase (www.pharmgkb.org/; Whirl-Carrillo et al. 2012).

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 or an LAI 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). A specific side effect (e.g., akathisia, weight gain, sedation, orthostatic hypotension, sexual dysfunction) may also have limited a patient's treatment adherence or ability to function in the past. If a patient has a concomitant physical condition (e.g., diabetes, cardiac conduction abnormalities, or a seizure disorder), choice of medication will need to consider the likelihood of exacerbating 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. 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.

Younger individuals who are experiencing a first episode of psychosis may be more likely to gain weight or develop adverse metabolic effects of antipsychotic medications (Correll et al. 2014; Jensen et al. 2019). This can influence selection of an initial medication. In such individuals, a lower initial medication dose may help in minimizing acute side effects of antipsychotic medication and improve a patient's willingness to continue with treatment (Czobor et al. 2015; Gaebel et al. 2010). Use of a lower initial medication dose is also reasonable because response may be more rapid and require a lower medication dose during a first episode of psychosis as compared to later episodes (Takeuchi et al. 2019). 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 based on pharmacokinetic considerations (Howard et al. 2000).

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 longer periods of time 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. Available evidence suggests that patients who have not exhibited at least a 20% reduction in symptoms (or minimal improvement) by about two weeks on a therapeutic dose are unlikely to be much improved at four to six weeks as reflected by at least a 50% reduction in symptoms (Samara et al. 2015). 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.

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 (Clozaril (clozapine) [product monograph] 2019). 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 (Clozaril (clozapine) [product monograph] 2019). Subsequent dose increases, if needed, should be of 100 mg or less, once or twice weekly. A slower rate of titration may be needed for patients with an initial episode of schizophrenia and in those who are older, severely debilitated, or sensitive to side effects. Those with a pre-existing central nervous system condition, including individuals with 22q11.2 deletion syndrome, also warrant a slower rate of titration and may have an increased risk of seizures at usual doses. Use of divided doses can be helpful in reducing side effects during initial dose titration although many patients are ultimately treated with a single dose at bedtime to minimize daytime sedation and facilitate adherence (Takeuchi et al. 2016). 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. Blood levels of clozapine can be helpful to obtain in making adjustments to clozapine doses. (See Statement 7.)

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)²⁹ 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/ μ L) occurs in the initial month of clozapine treatment (Myles et al. 2018), the frequency of ANC monitoring is also

²⁹ For Canadian prescribers, use the appropriate Canadian clozapine registry and not the U.S. Clozapine REMS program.

reduced with longer treatment duration. In patients who have stopped or interrupted treatment with clozapine for 30 days or more, the initial dose titration for clozapine and the monitoring frequency for treatment initiation should be followed.

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 parkinsonism and akathisia, are likely to persist with long-term treatment and additional approaches to management may be needed. (See Statements 12 and 13.)

If treatment is planned with an LAI antipsychotic medication, a trial of the same medication is usually given to assure tolerability. The conversion from an oral dose of medication to a corresponding dose of an LAI antipsychotic depends upon the specific medication (Meyer 2017), and product labelling for each medication describes approximate conversion ratios and whether a period of concomitant oral and LAI medication is needed.

Strategies to Address Initial Non-response or Partial Response to Antipsychotic Treatment

If a patient is showing response within several weeks of treatment initiation, continuing on the same medication and monitoring for continued improvement is appropriate. However, it is important to consider whether factors are present that would influence treatment response if there is no significant improvement after several weeks of treatment (e.g., <20% improvement in symptoms) or if improvement plateaus before substantial improvement is achieved (e.g., >50% improvement in symptoms, minimal impairment in functioning). Such factors may include concomitant substance use, rapid medication metabolism, poor medication absorption, interactions with other medications, or other effects on drug metabolism (e.g., smoking) that could affect blood levels of medication. Difficulties with adherence are a common contributor to reduced response. (See Statement 3 for a detailed discussion of adherence.) When adherence is poor or uncertain, use of an LAI formulation of an antipsychotic may improve adherence as well as response. Determination of the blood concentration of the drug may also be helpful if the patient is being treated with a medication (e.g., clozapine) for which blood level has some correlation with clinical response. For other antipsychotic medications, a blood level can help to determine if poor adherence or subtherapeutic levels may be contributing to poor response (Bishara et al. 2013; de Oliveira et al. 1996; Hiemke et al. 2004; Lopez and Kane 2013; McCutcheon et al. 2018; Melkote et al. 2018; Sparshatt et al. 2010; Uchida et al. 2011b; Van Putten et al. 1991). 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.

If no factors have been identified that would affect treatment response, 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 established (Samara et al. 2018), 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. Tables 5 through 6 can be consulted to identify antipsychotic medications with other receptor binding profiles or different side

effects. 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 and it can be helpful to advise patients of this possibility.

If a patient has had minimal or no response to two trials of antipsychotic medication of two to four weeks duration at an adequate dose (Howes et al. 2017; Samara et al. 2015), a trial of clozapine is recommended. (See Statement 7.) A trial of clozapine is also recommended for a patient with a persistent risk of suicide that has not responded to other treatments and is suggested for a patient with a persistent risk of aggressive behavior that has not responded to other treatments. (See Statements 8 and 9.) A trial of clozapine may also be appropriate in individuals who 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). In fact, clozapine is often underused (Carruthers et al. 2016; Latimer et al. 2013; Olfson et al. 2016; Stroup et al. 2014; Tang et al. 2017) and many patients would benefit from earlier consideration of clozapine initiation.

Augmentation treatment can also be considered, although a trial of clozapine should not be delayed by multiple attempts at augmentation therapy. Particularly for patients with negative symptoms or depression, augmentation of antipsychotic therapy with an antidepressant medication may also 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. In addition, if a patient experiences an exacerbation of symptoms while on a stable dose of medication, a reconsideration of the treatment plan is warranted rather than simply adding medications to the existing regimen.

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 or only a partial response to the most recently used medication.

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. (See Statement 3 for a detailed discussion of factors related to adherence.)

Monitoring of treatment response is also essential to identify whether there are reductions in the severity of functional impairments or target symptoms, including positive symptoms, negative symptoms, and other symptoms that are a focus of treatment. Use of a quantitative measure (see Statement 2) can assist in determining whether the antipsychotic medication is producing therapeutic benefits, including reductions in symptom severity and improvements in functioning. If a lack of response or a partial response is noted, additional assessment will be needed to identify and address possible contributors, as described above. If an antipsychotic medication dose is being decreased, monitoring can help detect a return of symptoms prior to a more serious relapse.

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). Still other side effects such as tardive dyskinesia, emerge only after longer periods of treatment or become more noticeable to patients as their acute symptoms are better controlled (e.g., sexual dysfunction). Table 2 in Statement 1 gives suggestions for baseline assessments and monitoring frequencies for some side effects, clinical measurements, and laboratory studies. Specific attention may need to be given to clinical workflow to assure that indicated monitoring is conducted because rates of follow-up testing and screening for metabolic side effects of treatment appears to be low (Morrato et al. 2009). 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 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 AIMS (Guy 1976) or the DISCUS (Kalachnik and Sprague 1993) can complement clinical assessment in identifying and monitoring tardive dyskinesia and other abnormal movements. 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.

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) can also be life-threatening because of associated hyperthermia and autonomic instability. It typically occurs within the first month of antipsychotic treatment, resumption of treatment, or with an increase in the dose of antipsychotic medication. Akathisia and medication-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 occur 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 or blood levels 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. Dermatological reactions, including hyperpigmentation and cutaneous reactions, have also been reported with risperidone, clozapine, olanzapine, quetiapine, and haloperidol (Bliss and Warnock 2013). 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. 2012, 2013b) and ensure that the patient is receiving treatment with a lipid-lowering agent, as clinically indicated.

Myocarditis and Cardiomyopathy

Myocarditis and cardiomyopathy have been reported in some 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 two 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 and troponin (I and T subtypes), and obtaining an electrocardiogram 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"). Though the Bazett formula remains most widely used for drug monitoring and research, alternative correction formulae, such as the Fridericia and Framingham formulae, have been shown to most accurately correct for rate and improve prediction of mortality. Clinicians should be familiar with an alternative correction formula to accurately predict risk (Aytemir et al. 1999; Rautaharju et al. 2009; Vandenberg et al. 2016). 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 et al. 2009), but the quality of data that informs such categorizations is also variable (Funk et al. 2018). Nevertheless, among the FGAs, chlorpromazine, droperidol, thioridazine, and pimozide 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 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 (Geodon 2018), quetiapine (Anonymous 2011; Seroquel XR 2019), iloperidone (Fanapt 2017), and paliperidone (Invega 2018, 2019; Invega Sustenna 2018a, 2018b; Invega Trinza 2018a, 2018b).

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 a 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 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. Nevertheless, treatment is not indicated unless the patient is symptomatic or the patient's heart rate is substantially greater than 120 bpm because 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 2015; Whicher et al. 2018; Zhang et al. 2017). 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; Polcwiartek 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, 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 link to antipsychotic-induced hyperprolactinemia has not been established (Bolton et al. 2017; Stubbs et al. 2014, 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 monitoring for constipation and, if present, constipation should be reported promptly to clinicians. 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; Palmer et al. 2008). 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) 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; Myles et al. 2019; Pisciotta 1969). For example, with chlorpromazine, transient benign leukopenia (white blood cell count $< 3,500/\text{mm}^3$) is common whereas severe neutropenia has been reported in 0.08% of patients, typically within the first few months of treatment (Pisciotta 1969).

There is no clear etiology of severe neutropenia or agranulocytosis, when most extreme. With clozapine, 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 severe neutropenia 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 severe neutropenia 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; Myles et al. 2017).

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; Koek and Pi, 1989). 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, ethnicity, recent cocaine use, high medication dose, and intramuscular route of medication administration (Gray and Pi 1998; Spina et al. 1993; van Harten et al. 1999). For further discussion of acute dystonia, including its treatment, see Statement 11.

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 Statement 13.

Parkinsonism

Medication-induced parkinsonism, which is termed neuroleptic-induced parkinsonism in DSM-5, is defined 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 medication-induced parkinsonism are dose dependent and generally resolve with discontinuation of antipsychotic medication. It is important to appreciate that medication-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 medication-induced parkinsonism. In addition, emotional and cognitive features of medication-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 medication-induced parkinsonism, including its treatment, see Statement 12.

Neuroleptic Malignant Syndrome

NMS is characterized by a classic triad of rigidity, hyperthermia,³⁰ and sympathetic 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, 2017). In addition, NMS is associated with an elevated level of serum creatine kinase (typically, at least four 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 conditions (American Psychiatric Association 2013a; Berman 2011; Rosebush and Stewart 1989; Strawn et al. 2007).

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 also may be increased by use of short-acting 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; Viejó et al. 2003). 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 of medication discontinuation 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

³⁰ >100.4°F or >38.0°C on at least two occasions, measured orally.

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 as well as at high blood levels or 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 for delineating the risks of a further seizure, determining whether anticonvulsant therapy (e.g., valproate) is indicated, and collaborating with the clinician 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 medication-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, 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; race/ethnicity; 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; Patterson-Lomba et al. 2019).

Although the majority of patients who develop tardive dyskinesia have mild symptoms, a small proportion will develop symptoms of moderate or severe degree. Tardive dyskinesia can have significant effects on quality of life and can be associated with social withdrawal (McEvoy et al. 2019). Although the impact appears to be influenced by the severity of tardive dyskinesia, individuals with mild symptoms can also experience negative effects on quality of life.

Evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinesic movements may be observed with a reduction in antipsychotic medication dose, which is termed a withdrawal-emergent dyskinesia (American Psychiatric Association 2013a). Fluctuations in symptoms are also common and may be influenced by factors such as psychosocial stressors. Furthermore, spontaneous dyskinesias, which are clinically indistinguishable from tardive dyskinesia, have been described in elderly patients, before the advent of antipsychotic medications and in up to 20% of never-medicated patients with chronic schizophrenia (Blanchet et al. 2004; Crow et al. 1982; 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 Statement 14.

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 can include impaired learning and memory and slowed cognition (Ang et al. 2017; Vinogradov et al. 2009).

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 antiparkinsonian medications, see Statement 12.

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, severe neutropenia, 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, as 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, increased sleep time, and reduced cognitive acuity, 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). The etiology of sialorrhea is unclear but may relate 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 (Dzahini et al. 2018; Kaplan et al. 2018; Stoecker et al. 2017). 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. Diphenhydramine has also been studied (Chen et al. 2019); 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).

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 six months of treatment, although some patients continue to gain weight indefinitely (Alvarez-Jimenez et al. 2008). In addition, younger individuals who are experiencing a first episode of psychosis may be more likely to gain weight with antipsychotic medication than older individuals (Correll et al. 2014; Jensen et al. 2019). 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; Gierisch et al. 2014; Mahmood et al. 2013; Manu et al. 2015; Mizuno et al. 2014; Mukundan et al. 2010; Vancampfort et al. 2019; 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 dietitians 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 (Bonfioli 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. 2016a; Vancampfort et al. 2019; Zheng et al. 2015; Zhuo et al. 2018). However, most studies have been small and follow-up periods have not been longer than six months. Modest benefit has also been seen in several studies of glucagon-like peptide-1 receptor agonists (Siskind et al. 2019) and small studies of topiramate (Mahmood et al. 2013; Mizuno et al. 2014; Vancampfort et al. 2019; Zhuo et al. 2018). 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 to change or augment treatment with a medication with lower weight-gain liability (Vancampfort et al. 2019). 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; Vancampfort et al. 2019). In any patient with weight gain, it is also important to assess for other contributors to metabolic syndrome (Mitchell et al. 2012, 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, 2019). 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 to overall health, improved cardiorespiratory fitness and other aspects of functioning (Dauwan et al. 2016; Firth et al. 2015, 2017; Vancampfort et al. 2017, 2019). Health promotion coaching interventions focused on individuals with mental illness, such as the In SHAPE program, can also be pursued and may be associated with weight loss and reduced cardiovascular risk (Bartels et al. 2015; Naslund et al. 2016; Van Citters et al. 2010; Verhaeghe et al. 2013).

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.

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 (Achtys 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 patients' 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, 2017c; 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; Remington 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 is offered or receives an initial prescription for antipsychotic treatment. An existing NQF endorsed measure (NQF #1879) "Adherence to Antipsychotic Medications for Individuals with Schizophrenia" is aimed at assessing whether an antipsychotic medication was continued once it was begun. 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 dispensed 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. It uses pharmacy claims data or electronic prescription orders to examine whether a medication has been prescribed, 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 or the medication dose and could be met through continuous prescriptions of a sub-therapeutic dose or clinically ineffective antipsychotic. Another limitation is the difficulty in determining the proportion of covered days in a 12 consecutive month period, particularly when patients have transitions in care between settings or treating clinicians.

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; Morrato et al. 2009). 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 Screening for People With Schizophrenia or Bipolar Disorder Who Are Prescribed Antipsychotic 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; however, before holding individual clinicians or facilities accountable for the delivered quality of care, the measures would need additional testing at these levels.

Statement 5: Continuing Medications

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

Implementation

For individuals with a diagnosis of schizophrenia whose symptoms have improved with an antipsychotic medication, there are a number of benefits to maintenance treatment including reduced risks of relapse (Bowtell et al. 2018; Goff et al. 2017; Hui et al. 2018; Kishi et al. 2019; Leucht et al. 2012; Thompson et al. 2018), rehospitalization (Tiihonen et al. 2018), and death (Tiihonen et al. 2018; Vermeulen et al. 2017). When administered on a long-term basis, however, antipsychotic medications are also associated with a greater incidence of weight gain, sedation, and movement disorders (Leucht et al. 2012). In addition, some studies have raised questions about whether long-term antipsychotic treatment might be associated with other adverse effects on functioning or health, including loss of brain volume (Davidson 2018; Goff et al. 2017). These data are heterogeneous and when compared to withholding treatment, there was minimal evidence to suggest negative effects of maintenance treatments on outcomes (Goff et al. 2017; Huhtaniska et al. 2017). In addition, these risks may be able to be mitigated by preventive interventions (e.g., early intervention for weight gain, screening for lipid and glucose abnormalities) and careful monitoring for side effects of medication. Nevertheless, as treatment proceeds the pluses and minuses of continuing on an antipsychotic medication should be reviewed with the patient in the context of shared decision-making. It will typically be beneficial to include family members or other persons of support in such discussions (Hamann and Heres 2019).

Despite the benefits of continued antipsychotic treatment for the majority of patients, maintaining adherence to an antipsychotic medication can be difficult (Acosta et al. 2012; Shafrin et al. 2016; Valenstein et al. 2006). Barriers, facilitators, and motivators of treatment adherence will differ for each patient. Engaging family members or other persons of support can be helpful in fostering adherence

* 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.

(Mueser et al. 2015). Other approaches to assessing and enhancing adherence are described in detail with Statement 3.

For some patients, the formulation of the antipsychotic medication may influence adherence. (See Table 3, 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 may be particularly useful for patients with a history of poor or uncertain adherence. (See Statement 10.)

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 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 (Essock et al. 2006). 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.

Evidence is limited on the rationale and approach to planned reductions of medication doses. Unless a medication requires emergent discontinuation, gradual reductions in doses are preferable with close monitoring for recurrent symptoms.

Shared decision-making discussions with the patient should consider the patient's recovery goals, the potential benefits of medication changes or dose reductions in terms of changes or diminution of side effects, and the potential harms of medication changes or dose reductions (Davidson 2018). The longitudinal course of the patient's episode and the certainty of their diagnosis should also be considered. There may be some individuals with a brief episode of psychosis or uncertain psychotic diagnosis (e.g., possible substance induced psychosis or mood-related psychosis) who may not require continuing antipsychotic treatment. On the other hand, individuals with chronic symptoms, repeated relapses, and clear diagnostic features of schizophrenia will likely have poorer outcomes if medications are stopped. In addition to symptom recurrence and relapse, medication cessation may be associated with hospitalization, legal difficulties, reduced likelihood of response with reinstatement of treatment, or poorer psychosocial outcomes (Correll et al. 2018; Hui et al. 2018; Takeuchi et al. 2019; Wilper et al. 2009). It will typically be beneficial to include family members or other persons of support in discussions of medication changes or dose reductions.

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 strength of research evidence). Long-term treatment with an antipsychotic medication has also been associated with a reduction in mortality as compared to no antipsychotic treatment in individuals with schizophrenia. 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 strength of research evidence).

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. Some studies have raised concerns about changes in brain region volumes with antipsychotic treatment, but these findings are heterogenous and inconsistent.

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 concerns about side effects, particularly weight gain, sedation, and restlessness that 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 and the long-term effects of antipsychotic medications are not well studied, the impact of schizophrenia on patient's lives is also substantial and consistent benefits of continued antipsychotic treatment were found. Overall, rates of mortality appear to be reduced by ongoing treatment with an antipsychotic medication as compared to no treatment. In addition, harms of treatment can be mitigated by using the lowest effective dose, 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 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

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 Statement 4 for a discussion of quality measures related to initiation and ongoing use of an antipsychotic medication.

Statement 6: Continuing the Same Medications

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 5, 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 an antipsychotic medication, including reduced risks of relapse (Bowtell et al. 2018; Goff et al. 2017; Hui et al. 2018; Kishi et al. 2019; Leucht et al. 2012; Thompson et al. 2018), rehospitalization (Tiihonen et al. 2018), and death (Tiihonen et al. 2018; Vermeulen et al. 2017). Implicitly, continued treatment with an effective and tolerable medication would be preferable to potential 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).

For these reasons, it will be optimal to continue on the same medication for most patients. Nevertheless, under some circumstances, it may be necessary to consider a change from one

* 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.

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. Another reason to change medications would be to initiate treatment with an LAI antipsychotic if the current oral medication is unavailable in an LAI formulation. (See Statement 10.) 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, 2013). Individuals who switched to aripiprazole, as compared to those who remained on their initial medication, had a higher rate of discontinuing treatment but showed no significant increases in symptoms or hospitalizations. In addition, the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) trial showed that individuals who experienced issues with medication efficacy or tolerability in an early phase of the trial 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, 2009). These findings suggest that a change in medication can be of benefit to patients under some circumstances but also suggest that the possible benefits and risks of a medication change should be reviewed with the patient in the context of shared decision-making. Such discussions with the patient should consider the patient's recovery goals, the potential benefits of medication changes or dose reductions in terms of changes or diminution of side effects, and the potential harms of medication changes or dose reductions (Davidson 2018). It will typically be beneficial to include family members or other persons of support in such discussions.

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 al. 2017a). 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. Depending upon the pharmacological properties of the medications, including pharmacokinetic and receptor binding profiles (see Tables 4 and 5), side effects of medications may also emerge (e.g., insomnia with a shift to a less sedating medication, withdrawal dyskinesia with a shift to a medication with less prominent dopamine D2 receptor blockade; Cerovecki et al. 2013).

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 6.)

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 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 7: Clozapine in Treatment-resistant Schizophrenia

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).

For the purpose of future research trials, 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 approach to establish minimum and optimum criteria for identifying treatment-resistant schizophrenia (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, or SANS and SAPS for symptoms and a score < 60 on the SOFAS as a measure of functioning). If a prospective medication trial of at least six 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 six 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, 2015; Rothe et al. 2018.) The consensus criteria include at least one antipsychotic blood level to assess adherence, obtaining information on adherence from at least two sources (e.g., pill counts, dispensing chart reviews,

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patient/carer reports), and obtaining information on past treatment response from patient/carer reports and other sources.

For clinical purposes, a common 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). However, if there is no significant improvement after several weeks of treatment (e.g., <20% improvement in symptoms), the likelihood of substantial improvement (e.g., >50% improvement in symptoms) is small (Howes et al. 2017; Samara et al. 2015) and a longer trial of the medication may not be warranted. It should also be noted that a medication trial cannot be viewed as adequate if truncated in terms of duration or dosage because of poor tolerability or if limited by poor adherence. Accordingly, some experts suggest a trial of an LAI antipsychotic medication before deciding that a patient's symptoms are treatment-resistant.

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. A trial of clozapine may also be appropriate in individuals who 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). In fact, clozapine is often underused (Carruthers et al. 2016; Latimer et al. 2013; Olsson et al. 2016; Stroup et al. 2014; Tang et al. 2017) and many patients would benefit from earlier consideration of clozapine initiation.

Discussion of clozapine should emphasize principles of shared decision-making; including family members or other persons of support in such discussions is often beneficial. In terms of a patient's recovery goals, most individuals value an ability to think more clearly and stop hallucinations or delusions in deciding about medication changes (Achtyes et al. 2018). In addition, 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 (Siskind et al. 2017a). 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 (Daod et al. 2019; Farooq et al. 2019; Gee et al. 2017; Kelly and Love 2019; Kelly et al. 2018; Leung et al. 2019; 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 (Clozaril (clozapine) [product monograph] 2019). 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 (Clozaril (clozapine) [product monograph] 2019). 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 with an initial episode of schizophrenia and in those who are older, severely debilitated, or sensitive to side effects. Those with a pre-existing central nervous system condition, including individuals with 22q11.2 deletion syndrome, also warrant a slower rate of titration and may have an increased risk of seizures at usual doses. Use of divided doses can be helpful in reducing side effects during initial dose titration although many patients are ultimately treated with a single dose at bedtime to minimize daytime sedation and facilitate adherence (Takeuchi et al. 2016).

Monitoring for therapeutic benefits and side effects of clozapine should occur throughout the dose titration phase. (See 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 of 48 hours or more, 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 is useful to obtain blood levels of clozapine and its major active metabolite, norclozapine (n-desmethylclozapine) (Couchman et al. 2010). Blood 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 blood 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; Stark and Scott 2012; 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 blood level of clozapine.

As with the results of any laboratory test, interpretation of clozapine 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.

Typically, the level of norclozapine will be reported along with the blood level of clozapine. Norclozapine is the major active metabolite of clozapine and appears to differ from clozapine in efficacy and side effects. Nevertheless, the value of norclozapine levels in guiding clinical decisions is unclear. Because the half-life of norclozapine is greater than the half-life of clozapine, a clozapine:norclozapine ratio of less than 0.5 can suggest poor adherence over the previous day or rapid metabolism of clozapine (e.g., via CYP1A2 induction). A clozapine:norclozapine ratio of greater than 3.0 could suggest that metabolic pathways are saturated or inhibited by a concomitant medication. Shifts in the ratio of clozapine:norclozapine can also result from other drug-drug interactions or if non-trough levels are obtained (Couchman et al. 2010; Ellison and Dufresne, 2015).

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.³¹ 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

³¹ For Canadian prescribers, use the appropriate Canadian clozapine registry and not the U.S. Clozapine REMS program.

30 days or more, the initial dose titration for clozapine and the monitoring frequency for treatment initiation should be followed.

Because the highest risk of severe neutropenia (ANC <500/ μ L) occurs in the initial six months of clozapine treatment (Alvir et al. 1993; 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 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 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.

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, severe neutropenia, 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) 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. 2008; Leucht et al. 2013; Zhang et al. 2013), hyperlipidemia (Buhagiar and Jabbar 2019; 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 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. 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 six months of treatment, although some patients continue to gain weight indefinitely (Alvarez-Jimenez et al. 2008). 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 five 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 behavioral 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; McGinty et al. 2016; Mizuno et al. 2014; Siskind et al. 2016a; Vancampfort 2019; Zheng et al. 2015; Zhuo et al. 2018). Fewer studies have been done with glucagon-like peptide-1 agonist medications, but the available data suggest that body weight and metabolic risk factors are reduced by these medications as compared with placebo (Siskind et al. 2019). 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 2019; 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, 2017; Vancampfort 2019; Vancampfort et al. 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, as 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 titration), 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 (Dzahini et al. 2018; Kaplan et al. 2018; Stoecker et al. 2017). 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). Diphenhydramine has also been studied (Chen et al. 2019); 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. Nevertheless, treatment is not indicated unless the patient is symptomatic or the patient's heart rate is substantially greater than 120

bpm because 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, medication-induced parkinsonism, NMS, tardive syndromes, hyperprolactinemia) can occur but are less frequent with clozapine than with many other antipsychotic medications. (See 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 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 for psychosis (CBTp) as recommended in Statement 16 or initial benefits of CBTp may have faded if CBTp was stopped. Under such circumstances, treatment with CBT may be warranted (Burns et al. 2014; Morrison et al. 2018). Engaging families or persons of support in CBTp can also be helpful (Turkington and Spencer 2019). 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 eight 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 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

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.

2019a). 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.

Augment Clozapine or Another Antipsychotic Medication with Electroconvulsive Therapy

There is also evidence for benefits of ECT in combination with clozapine as compared to clozapine alone in most (Ahmed et al. 2017; Grover et al. 2015; Lally et al. 2016b; Petrides et al. 2015; Pompili et al. 2013; G. Wang et al. 2018), but not all (Melzer-Ribeiro et al. 2017), studies. 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.

Some studies have shown evidence for benefits of ECT in combination with antipsychotic medications other than clozapine (Ahmed et al. 2017; Ali et al. 2019; Pompili et al. 2013; Sinclair et al. 2019; 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 research evidence) as well as lower rates of self-harm, suicide attempts, or hospitalizations to prevent suicide (moderate strength of research evidence). Overall rates of hospitalization are also reduced during treatment with clozapine as compared to other oral antipsychotic medications (low strength of research evidence). All-cause mortality is also reduced in individuals treated with clozapine as compared to other individuals with treatment-resistant schizophrenia (moderate strength of research evidence).

Harms

Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low strength of research evidence), clozapine does have a higher risk of study withdrawal due to adverse events than some other SGAs (low strength of research evidence). 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 (Achtys 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 (Achtys 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 (Siskind et al. 2017a). In contrast, most other antipsychotic medications were viewed less positively (Siskind et al. 2017a). In addition, in the CATIE study, clozapine and combination antipsychotic treatment regimens were frequently selected by patients by those who stopped the previous medication due to inadequate therapeutic effect and by those with relatively severe symptoms (Stroup et al. 2009).

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. 2019; 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, Statement 7.)

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 schizophrenia, 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 clozapine is underused and 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; Bachmann et al. 2017; Carruthers et al. 2016; Keller et al. 2014; Olfson et al. 2016; Stroup et al. 2014; Tang et al. 2017). 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 (i.e., rating scales) to improve identification of individuals with treatment-resistant schizophrenia and facilitate systematic longitudinal tracking of functioning, symptoms, and side effect burdens. If quality measures are considered for development at the provider, facility, health plan-, integrated delivery system-, or population-level, testing of feasibility, usability, reliability, and validity would be essential prior to use for purposes of accountability.

Electronic decision support would be challenging to implement and would depend on accurate and consistent entry of structured information. Nevertheless, in combination with rating scale data and prior prescribing histories, electronic decision support could help identify individuals with treatment-resistant illness who would benefit from a trial of clozapine.

Statement 8: Clozapine in Suicide Risk

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 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 Statement 3 for additional details.) As in other circumstances in which patients do not appear to be responding fully to treatment, attention to adherence is crucial. (See Statement 3 for additional details.) For details of initiating and monitoring clozapine treatment, see Statement 7 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 strength of research evidence). Additional benefits of clozapine treatment include higher rates of treatment response (low to moderate strength of research evidence) and reductions in psychotic symptoms, all-cause mortality, overall hospitalization rates, and treatment discontinuation due to lack of efficacy (low to moderate strength of research evidence).

Harms

Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low strength of research evidence), clozapine does have a higher risk of study withdrawal due to adverse events than some other SGAs (low strength of research evidence). 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 (Achtys 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 (Achtys 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 (Siskind et al. 2017a). 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, 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

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 clozapine is underused and 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; Bachmann et al. 2017; Carruthers et al. 2016; Keller et al. 2014; Olfson et al. 2016; Stroup et al. 2014; Tang et al. 2017). Given low utilization of clozapine, in general (Addington et al. 2012; Bachmann et al. 2017; Carruthers et al. 2016; Keller et al. 2014; Olfson et al. 2016; Stroup et al. 2014; Tang et al. 2017), 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.

If quality measures are considered for development at the provider, facility, health plan-, integrated delivery system-, or population-level, testing of feasibility, usability, reliability, and validity would be essential prior to use for purposes of accountability. In particular, it is currently not possible to identify people at increased risk for suicide from most administrative data. Clinical assessment or patient self-report data are likely to be required.

Electronic decision support using passive alerts may be able to prompt clinicians to consider clozapine; however, such prompts would be challenging to implement as they would depend on accurate and consistent entry of structured information about diagnosis, suicidal ideation, and suicide attempts. Nevertheless, in combination with rating scale data, electronic decision support could help identify individuals with schizophrenia and significant suicide risk who would benefit from a trial of clozapine.

Statement 9: Clozapine in Aggressive Behavior

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. As in other circumstances in which patients do not appear to be responding fully to treatment, attention to adherence is crucial. (See Statement 3 for additional details.) Risk factors for aggressive behavior in individuals with schizophrenia are described under 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 Statement 3 for additional details.) For details of initiating and monitoring clozapine treatment, see Statement 7 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 strength of research evidence). Additional benefits of clozapine treatment include higher rates of treatment response (low to moderate strength of research evidence); reductions in psychotic symptoms, all-cause mortality, overall hospitalization rates, and treatment discontinuation due to lack of efficacy (low to moderate strength of research evidence); and lower rates of self-harm, suicide attempts, or hospitalizations to prevent suicide (moderate strength of research evidence).

Harms

Although overall rates of adverse events do not differ with clozapine as compared to risperidone (low strength of research evidence), clozapine does have a higher risk of study withdrawal due to adverse

* 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.

events than some other SGAs (low strength of research evidence). 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 (Achtys 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 (Achtys 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 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, 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. 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 for purposes of accountability. Electronic decision support using passive alerts may be able to prompt clinicians to consider clozapine; however, such prompts would be challenging to implement as they would depend on accurate and consistent entry of structured information about diagnosis and risk factors for aggression. Nevertheless, in combination with rating scale data, electronic decision support could help identify individuals with schizophrenia and significant aggression risk who may benefit from a trial of clozapine.

Statement 10: Long-acting Injectable Antipsychotic Medications

APA suggests (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*

Implementation

LAI formulations of antipsychotic medications can provide a number of benefits for patients, families, and clinicians yet they are often underutilized (Brown et al. 2014; Correll et al. 2016; Lawson et al. 2015; Sultana et al. 2019). Racial differences also exist in the proportion of individuals who are treated with LAI antipsychotic medications with greater use of these formulations in black as compared to white patients (Brown et al. 2014; Lawson et al. 2015).

With LAI antipsychotic medications, there is greater assurance that a patient will receive medication continuously as there are fewer opportunities to miss a medication dose and clinicians will be immediately aware of a missed visit or injection, yielding greater time for intervention before symptoms recur (Correll et al. 2016; Velligan et al. 2010; West et al. 2008). Presumably due to improved adherence, advantages of LAI antipsychotics include the potential for a decreased risk of mortality, reduced risk of hospitalization, and decreased rates of treatment discontinuation, including discontinuation due to inefficacy. (See Appendix C, Statement 10.) Other benefits for patients include a subjective sense of better symptom control, greater convenience as a result of needing to take fewer medications daily, and reduced conflict with family members or other persons of support related to medication-related reminders (Caroli et al. 2011; Correll et al. 2016; Iyer et al. 2013; Yeo et al. 2019). Although some patients may not wish to experience the discomfort associated with receiving injections of medications, this is not a major barrier for most patients. In addition, discomfort can often be minimized by using SGA LAIs rather than FGA LAIs, which have sesame oil-based vehicles, or by using an LAI with a small injection volume or lower administration frequency (Correll et al. 2016).

* 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.

Consistent with principles of patient-centered care, it may be preferable to educate patients about the availability of LAI antipsychotic medications when discussing other aspects of antipsychotic treatment. Indeed, many patients will accept and may prefer LAIs if provided with information about the pluses and minuses of LAIs in the context of shared decision-making (Caroli et al. 2011; Heres et al. 2007; Kane et al. 2019; Waddell and Taylor 2009; Weiden et al. 2015; Yeo et al. 2019). Preference rates for LAIs are even higher among individuals who have personal experience in receiving an LAI formulation of an antipsychotic medication (Heres et al. 2007; Patel et al. 2009; Waddell and Taylor 2009).

Discussions about LAI antipsychotic medications often occur in patients who have had difficulty in adhering to oral medications. However, such discussions can also take place at other junctures. For example, if an individual has not responded to treatment with an oral antipsychotic medication, a trial of an LAI may be warranted (Howes et al. 2017; see Statement 4, Strategies to Address Initial Non-response or Partial Response to Antipsychotic Treatment) because breaks in the continuity of oral medication therapy can be unrecognized (Lopez et al. 2017). An LAI formulation of an antipsychotic may also be considered when patients are transitioning between settings (e.g., at inpatient discharge, upon release from a correctional facility) when future adherence is uncertain and the risk of reduced adherence may be increased. Although LAI antipsychotic medications have typically been used in individuals with multiple episodes of schizophrenia, some studies have used an LAI antipsychotic formulation earlier in the course of illness (Kane et al. 2019; Subotnik et al. 2015) when rates of poor adherence may be greater. Earlier discussion of an LAI may also be considered in individuals who are at increased risk of poor adherence due to a limited awareness of needing treatment or a co-occurring substance use disorder (Garcia et al. 2016; Velligan et al. 2009).

If a decision is made to initiate treatment with an LAI, aspects of medication selection are similar to those for selection of an oral medication in terms of considering prior response, prior tolerability, pharmacological considerations, and side effect profiles. (See Statement 4.) Patients may also have specific preferences and values related to the frequency of injection and the type and location of the injection (e.g., IM deltoid or gluteal sites, subcutaneous abdominal site) (Heres et al. 2012). Because the oral and LAI formulations of a specific antipsychotic medication are comparable, a trial of the same oral antipsychotic will typically occur first to assure efficacy and tolerability (SMI Adviser 2019). Patients will experience medication side effects for a longer period of time after drug discontinuation with LAIs than with oral medications due to pharmacokinetic differences in the formulations, but this is not usually a problem if the oral formulation has first been well tolerated. Nevertheless, caution is warranted in a patient who has experienced NMS previously (Correll et al. 2016).

The conversion from an oral dose of medication to a corresponding dose of an LAI antipsychotic depends upon the specific medication (see Tables 7, 8, and 9 on LAI antipsychotic medications; Meyer 2013, 2017); product labelling for each medication describes approximate conversion ratios and whether a period of concomitant oral and LAI medication is needed. If the patient is taking an oral medication that lacks a corresponding LAI formulation, a change in antipsychotic medication may be needed if an LAI formulation is clinically indicated or preferred. (See Statement 6.)

When administering LAI antipsychotic injections, it is important to follow recommendations for safe injection practices (Centers for Disease Control and Prevention 2019a, 2019c) and infection control

precautions (Centers for Disease Control and Prevention 2016, 2019c) as well as instructions from product labelling. Product labelling also contains important information on storage and reconstitution of LAI antipsychotic formulations as well as information on how to handle missed or late doses of medications. (See Tables 7-9.)

There are several barriers related to the use LAI formulations of antipsychotic medications. For patients, there may be logistical barriers (e.g., transportation, childcare, school or work schedules) that depend upon the frequency of appointments needed to receive an LAI antipsychotic medication. Other logistical barriers for patients may relate to factors such as cost or insurance authorizations for LAI antipsychotic agents. For clinicians, lack of knowledge and limited experience in using LAI antipsychotic medications contribute to underuse (Correll et al. 2016). Skill and experience in administering injections may be lacking and nursing staff may not be available to give injections. Additional barriers relate to the decision to suggest an LAI antipsychotic medication. Clinicians often do not consider LAI antipsychotic medications as a treatment option (Hamann et al. 2014; Heres et al. 2006; Kirschner et al. 2013; Weiden et al. 2015), even when such use is appropriate. Furthermore, clinicians may overestimate patients' adherence with oral medications in considering relative benefits of LAIs (Correll et al. 2016; Lopez et al. 2017) or underestimate the acceptability of LAIs to patients (Hamann et al. 2010; Iyer et al. 2013; Patel et al. 2010a, 2010b; Weiden et al. 2015). At an organizational level, there may be a lack of resources, space, or trained personnel to administer injections (Velligan et al. 2011; Correll et al. 2016). Thus, workflows may need to be adjusted, partnerships developed with primary care clinicians to administer LAI antipsychotic injections, or other concerted efforts may be needed to address logistical and clinical barriers to LAI antipsychotic use.

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

Benefits

Use of an LAI antipsychotic medication in the treatment of schizophrenia may be associated with improved outcomes. Although meta-analyses of head-to-head RCTs comparing LAI to oral antipsychotic (McDonagh et al. 2017) and other meta-analyses of RCTs (Kishi et al. 2016a, 2016b; Kishimoto et al. 2014; Ostuzzi et al. 2017) do not show evidence of benefit from LAIs relative to oral antipsychotic medications, observational data from nationwide registry databases (Taipale et al. 2018a, 2018b; Tiihonen et al. 2011, 2017), cohort studies (Kishimoto et al. 2018), and "mirror image" studies (Kishimoto et al. 2013) suggest that use of LAI antipsychotic agents as compared to oral antipsychotic medications are associated with a decreased risk of mortality, reduced risk of hospitalization, and decreased rates of study discontinuation (including discontinuation due to inefficacy).

Harms

The harms of using an LAI antipsychotic medication in the treatment of schizophrenia are generally comparable to the harms of using an oral formulation of the same medication. For some patients, side effects may be less problematic because peaks and troughs of medication levels will be less prominent than with oral medications due to the pharmacokinetic differences in the medication formulations. On the other hand, patients may experience medication side effects for a longer period of time with LAIs than with oral medications, again due to pharmacokinetic differences. In addition, patients may

experience Injection-related side effects including pain, swelling, redness, or induration at the injection site with LAI antipsychotic agents.

Patient Preferences

Clinical experience suggests that many patients are cooperative with and accepting of an LAI antipsychotic medication as part of a treatment plan, particularly when the option of an LAI and the pluses and minuses of an LAI antipsychotic are reviewed in the context of shared decision-making (Caroli et al. 2011; Heres et al. 2007; Kane et al. 2019; Waddell and Taylor 2009; Weiden et al. 2015; Yeo et al. 2019). Attitudes about LAIs are typically more positive among patients who have previously received or currently receive an LAI antipsychotic medication than in those who have never been treated with an LAI medication (Patel et al. 2009). Many patients prefer the convenience of receiving an infrequent injection rather than needing to remember to take oral medications. They also value the potential benefits of an LAI antipsychotic medication in terms of better subjective symptom reduction or improved long-term outcomes. On the other hand, some patients may not wish to experience the discomfort associated with receiving injections of medications.

Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as likely to outweigh the potential harms. The outcomes associated with use of an LAI formulation of an antipsychotic medication are at least as good as using an oral formulation of the medication and may be better, particularly in terms of treatment discontinuation, rehospitalization, and mortality risk. Many experts infer that the relative benefits of LAI antipsychotic medications as compared to equivalent oral formulations are related to improved adherence with LAI antipsychotics (Velligan et al. 2010; West et al. 2008), although specific data to test this supposition are not available. Nevertheless, use of an LAI antipsychotic may have additional advantages in patients who have difficulty with adherence or in whom adherence is uncertain. The side effects of treatment with an LAI antipsychotic medication are also comparable to side effects with the corresponding oral medication. (For additional discussion of the research evidence, see Appendix C, Statement 10.)

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 (Barnes et al. 2011; Buchanan et al. 2010; Galletly et al. 2016; Hasan et al. 2012; National Institute for Health and Care Excellence 2014; Remington et al. 2017; Scottish Intercollegiate Guidelines Network 2013). Other guidelines on the treatment of schizophrenia suggest use of LAIs based on patient preference (BAP, CSG, NICE, PORT, RANZCP, SIGN) or in the context of poor or uncertain adherence (BAP, NICE, RANZCP, SIGN). The RANZCP and WFSBP guidelines also note that LAIs should be considered if there has been a poor response to oral medication and the RANZCP guideline notes that LAIs should be offered to patients early in the clinical course of schizophrenia.

Quality Measurement Considerations

As a suggestion, this guideline statement is not appropriate for use as a quality measure. However, only a small proportion of individuals with schizophrenia receive an LAI antipsychotic medication in clinical practice (Brown et al. 2014; Correll et al. 2016; Lawson et al. 2015; Sultana et al. 2019). Because adherence is poor or uncertain in many individuals with schizophrenia, other patients may benefit from or prefer to receive an LAI antipsychotic medication if one is offered. Consequently, electronic decision support could suggest that clinicians consider an LAI antipsychotic medication if poor adherence is documented or with repeated hospitalizations or emergency visits. In addition, health care organizations may wish to assure that they will provide treatment with an LAI antipsychotic medication to patients when appropriate. Health care organizations and health plans may also wish to implement internal process measures to assess and increase rates at which LAI antipsychotics are used.

Statement 11: Anticholinergic Medications for Acute Dystonia

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; Koek and Pi, 1989). 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, ethnicity, recent cocaine use, high medication dose, and intramuscular route of medication administration (Gray and Pi 1998; 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 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. After several weeks to months, anticholinergic medications can sometimes be reduced or withdrawn without recurrence of dystonia or worsening of other antipsychotic-induced neurological symptoms (Desmarais et al. 2012). 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 can include impaired learning and memory and slowed cognition (Ang et al. 2017; Vinogradov et al. 2009). 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. Nevertheless, the long-term benefits and harms of anticholinergic medications are less clear and, in this context, harms may outweigh benefits. (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 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. Even with short-term treatment, some patients could have the potential to develop significant anticholinergic side effects, which would need to be incorporated into exclusion and exemption criteria. With reductions in the use of high doses of high-potency FGAs, the frequency of acute dystonia is significantly reduced. Any measure would only apply to a small number of individuals, which would complicate testing for feasibility, usability, reliability, and validity.

Statement 12: Treatments for Parkinsonism

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

Medication-induced parkinsonism, termed neuroleptic-induced parkinsonism in DSM-5, is defined 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 medication-induced parkinsonism are dose dependent and generally resolve with discontinuation of antipsychotic medication. It is important to appreciate that medication-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 medication-induced parkinsonism. In addition, emotional and cognitive features of medication-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 medication-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.) For individuals who are highly sensitive to medication-induced parkinsonism, clozapine may be considered. 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 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 medication-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.

Parkinsonism should also be distinguished from tardive dyskinesia, which can be worsened by use of anticholinergic medications (Bergman and Soares-Weiser 2018; Cogentin 2013).

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. After several weeks to months, anticholinergic medications can sometimes be reduced or withdrawn without recurrence of parkinsonism or worsening of other antipsychotic-induced neurological symptoms (Desmarais et al. 2012). Medications with anticholinergic effects can result in multiple difficulties for patients, including impaired quality of life, impaired cognition, 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 Medication-Induced Parkinsonism ^{32,33}

Generic name	Amantadine	Benztropine mesylate	Diphenhydramine	Trihexyphenidyl hydrochloride
Trade name ³⁴	Symmetrel	Cogentin	Benadryl	Artane
Typical use	Parkinsonism	Acute dystonia, parkinsonism	Acute dystonia, parkinsonism	Acute dystonia, parkinsonism
Mechanism of action	Uncompetitive NMDA receptor antagonist (weak)	Muscarinic antagonist	Histamine H1 antagonist	Muscarinic antagonist
Available formulations (mg, unless otherwise noted)	Tablet: 100 Tablet, Extended Release: 129, 193, 258 Capsule: 100 Capsule, Liquid Filled: 100 Capsule, Extended Release: 68.5, 137 Oral Syrup: 50/5 mL	Tablet: 0.5, 1, 2 Solution, Injection: 1/mL (2 mL)	Capsule: 25, 50 Oral Elixir: 12.5/5 mL Oral Solution: 12.5/5 mL, 6.25 /1 mL Tablet: 25, 50 Solution, Injection: 50/1 mL Other brand name formulations are available for allergy relief	Oral Elixir: 0.4 /mL (473 mL) Tablet: 2, 5
Typical dose range (mg/day)	Immediate Release Tablet or Capsule: 100-300 Extended Release Tablet: 129-322	Tablet: 0.5-6.0 Solution, Injection: 1-2	Oral: 75-200 Solution, Injection: 10-50	Oral: 5-15

³² This table includes information compiled from multiple sources. Detailed information on issues such as dose regimen, dose adjustments, medication administration procedures, handling precautions, and storage can be found in product labeling. It is recommended that readers consult product labeling information for authoritative information on these medications.

³³ *Source:* Amantadine hydrochloride capsules 2015; Amantadine hydrochloride oral solution 2015; Amantadine hydrochloride tablets 2019; Benadryl 2018; Bzotropine injection 2017; Bzotropine tablets 2017; Cogentin 2013; Diphenhydramine hydrochloride injection 2019; Lexicomp 2019; Micromedex 2019; Procyshyn et al. 2019; Trihexyphenidyl hydrochloride oral solution 2010; Trihexyphenidyl hydrochloride tablets 2015

³⁴ 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.

Generic name	Amantadine	Benztropine mesylate	Diphenhydramine	Trihexyphenidyl hydrochloride
Bioavailability	86% to 94%	29%	40% to 70%	100%
Time to peak level (hours)	Immediate Release: 2-4 Extended Release: 7.5-12	Oral: 7 IM: minutes	1-4	1.3
Protein binding	67%	95%	76% to 85%	Not known
Metabolism	Primarily renal	Hepatic	Hepatic	Not known
Metabolic enzymes/transporters	Substrate of organic cation transporter 2	Substrate of CYP2D6 (minor)	Extensively hepatic n-demethylation via CYP2D6; minor demethylation via CYP1A2, CYP2C9 and CYP2C19. Inhibits CYP2D6 (weak).	None known
Metabolites	Multiple; unknown activity	Not known	Inactive	
Elimination half-life (hours)	16-17	7	4-8	4
Excretion	Urine 85% unchanged; 0.6% fecal	Urine	Urine (as metabolites and unchanged drug)	Urine and bile
Hepatic impairment	No dose adjustments noted in labeling	No dose adjustments noted in labeling	No dose adjustments noted in labeling	No dose adjustments noted in labeling
Renal impairment	Elimination half-life increased with renal impairment.	No dose adjustments noted in labeling	No dose adjustments noted in labeling; however, dosing interval may need to be increased or dosage reduced in older individuals and with renal impairments	No dose adjustments noted in labeling

Generic name	Amantadine	Benztropine mesylate	Diphenhydramine	Trihexyphenidyl hydrochloride
Comments	Negligible removal by dialysis; do not crush or divide extended release products.	Onset of action with IV is comparable to IM.	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.	

Abbreviations: IM=intramuscular; IV=intravenous; NMDA= N-methyl-D-aspartate

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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 can include impaired learning and memory and slowed cognition (Ang et al. 2017; Vinogradov et al. 2009). 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 medication-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 medication-induced parkinsonism than anticholinergic agents (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). With the absence of anticholinergic properties, side effects including cognitive impairment are less prominent with amantadine than with anticholinergic agents. 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 medication-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 medication-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 medication-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 medication-induced parkinsonism is 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 medication-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 medication-induced parkinsonism has associated risks and characteristics and preferences of each patient need to be taken into consideration. In addition, the long-term benefits and harms of anticholinergic medications are less clear and harms of long-term use may outweigh benefits. (For additional discussion of the research evidence, see Appendix C, Statement 12.)

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 medication-induced parkinsonism. The WFSBP guideline notes that use of SGAs or reductions in medication doses should be the primary treatment for medication-induced parkinsonism (Hasan et al. 2013). The BAP guideline notes that decisions about the use of anticholinergic medications for medication-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 13: Treatments for Akathisia

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.) 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 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; Poyurovsky and Weizman 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 13.)

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 14: VMAT2 Medications for Tardive Dyskinesia

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).

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 medication-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, 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; race/ethnicity; 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; Patterson-Lomba et al. 2019).

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). Fluctuations in symptoms are also common and may be influenced by factors such as psychosocial stressors. Furthermore, spontaneous dyskinesias, which are clinically indistinguishable from tardive dyskinesia, have been described in elderly patients before the advent of antipsychotic medications and in up to 20% of never-medicated patients with chronic schizophrenia (Blanchet et al. 2004; Crow et al. 1982; 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.) The AIMS and the DISCUS are examples of such tools (Guy 1976; Kalachnik and Sprague 1993; Munetz and Benjamin 1988). When using scales such as the AIMS or the DISCUS, it should be noted that there is no

specific score threshold that suggests a need for intervention although ranges of scores are noted to correspond with mild, moderate, and severe symptoms. In addition, the same total score can be associated with significantly different clinical manifestations and a varying impact on the patient. Patients, family members, and other persons of support may be able to provide information about the onset of movements, their longitudinal course in relationship to treatment or other precipitants, and their impact on functioning, health status (including dentition), and quality of life.

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, 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). Treatment with a VMAT2 inhibitor can also be considered for patients with mild tardive dyskinesia based on factors such as patient preference, associated impairment, or effect on psychosocial functioning. 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^{35,36}

Generic name	Deutetrabenazine	Tetrabenazine	Valbenazine
Trade name ³⁷	Austedo	Xenazine	Ingrezza
Available formulations (mg)	Tablet: 6, 9, 12	Tablet: 12.5, 25	Capsule: 40, 80
Typical dose range (mg/day)	12-48	25-75	40-80
Bioavailability	80%	75%	49%

³⁵ This table includes information compiled from multiple sources. Detailed information on issues such as dose regimen, dose adjustments, medication administration procedures, handling precautions, and storage can be found in product labeling. It is recommended that readers consult product labeling information for authoritative information on these medications.

³⁶ Source. Austedo tablets 2019; Ingrezza 2019; Lexicomp 2019; Micromedex 2019; Xenazine tablets 2018

³⁷ 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.

Generic name	Deutetrabenazine	Tetrabenazine	Valbenazine
Time to peak level (hours)	3-4	1-2	0.5-1
Protein binding	60% to 68% (alpha-HTBZ) 59% to 63% (beta-HTBZ)	82% to 85% 60% to 68% (alpha-HTBZ) 59% to 63% (beta-HTBZ)	>99% 64% alpha- HTBZ
Metabolism	Hepatic	Hepatic	Hepatic
Metabolic enzymes/transporters	Major substrate of CYP2D6, minor substrate of CYP1A2 and CYP3A4	Major substrate of CYP2D6	Major substrate of CYP3A4, minor substrate of CYP2D6
Metabolites	Deuterated alpha and beta HTBZ: Active	Alpha, beta and O-dealkylated HTBZ: Active	alpha- HTBZ: Active
Elimination half-life (hours)	Deuterated alpha and beta HTBZ: 9-10	Alpha-HTBZ: 4-8 Beta-HTBZ: 2-4	15-22
Excretion	Urine (~75%-85% changed); feces (~8% to 11%)	Urine (~75% changed); feces (~7% to 16%)	Urine: 60%; feces: 30%
Hepatic impairment	Contraindicated	Contraindicated	Maximum dose of 40mg daily with moderate to severe impairment (Child-Pugh score 7 to 15)
Renal impairment	No information available	No information available	Use not recommended in severe renal impairment (CrCl <30 mL/min)
Common adverse effects	Sedation	Sedation, depression, extrapyramidal effects, insomnia, akathisia, anxiety, nausea, falls	Sedation
Effect of food on bioavailability	Food effects maximal concentration. Administer with food. Swallow tablets whole and do not chew, crush, or break.	Unaffected by food	Can be taken with or without food. High fat meals decreased the Cmax and AUC for valbenazine but values for the active metabolite (alpha-HTBZ) are unchanged

Generic name	Deutetrabenazine	Tetrabenazine	Valbenazine
Comments ³⁸	Give in divided doses, increase from initial dose of 12 mg once 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. Assess ECG before and after increasing the daily dose above 24 mg in patients at risk for QTc prolongation. Avoid use in patients with congenital long QT syndrome, with arrhythmias associated with a prolonged QT interval or other risks for QTc prolongation (e.g., drugs known to prolong QTc intervals, reduced metabolism via CYP 2D6).	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 > 50 mg/day. Do not exceed 50 mg/day in poor metabolizers or in patients treated with a strong inhibitor of CYP2D6. Avoid use in patients with congenital long QT syndrome, with arrhythmias associated with a prolonged QT interval or other risks for QTc prolongation (e.g., drugs known to prolong QTc intervals, reduced metabolism via CYP 2D6).	Initiate at 40 mg once daily and increase to 80 mg once daily after 1 week. Continuation of 40 mg once daily may be considered for some patients. 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 congenital long QT syndrome, with arrhythmias associated with a prolonged QT interval or other risks for QTc prolongation (e.g., drugs known to prolong QTc intervals, reduced metabolism via CYP 2D6 or CYP3A4).

Abbreviations: CrCl=creatinine clearance; HTBZ=dihyrotetrabenazine; QTc=corrected QT interval

In general, deutetrabenazine or valbenazine are preferred over tetrabenazine because of the greater evidence base supporting their use. In addition, tetrabenazine has a shorter half-life and greater rates of associated depression when used in the treatment of patients with Huntington disease. 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).

³⁸ 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.

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. A lower dose of antipsychotic medication can be considered, although evidence for this approach is minimal (Bergman et al. 2017) and the potential for benefit needs to be weighed against the possibility of recurrent symptoms or relapse. 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 a lower potency medication and particularly to clozapine may also be associated with a reduction in tardive dyskinesia, particularly for individuals with moderate to severe symptoms (Mentzel et al. 2018). Again, however, the potential benefits of changing medication should be considered in light of the possibility of symptom recurrence.

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. Anticholinergic medications do not improve and may even worsen tardive dyskinesia (Bergman and Soares-Weiser 2018; Cogentin 2013) in addition to producing significant side effects.

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; Kiriakakis et al. 1998). 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 (Burke et al. 1982; Kang et al. 1986; Wojcik et al. 1991), although these medications are not useful in treating tardive dyskinesia (Bergman and Soares-Weiser 2018; Cogentin 2013). 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 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

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

If a quality measure on VMAT2 inhibitor treatment of tardive syndromes is considered at the provider, facility, health plan-, integrated delivery system-, or population-level, testing of feasibility, usability, reliability, and validity would be essential prior to use for purposes of accountability. However, it may be possible and preferable to incorporate this recommendation into internal facility or health plan initiatives focused on enhanced identification and treatment of tardive syndromes.

Electronic decision support using passive alerts may be able to prompt clinicians to consider a VMAT2 inhibitor, although such prompts would depend on accurate and consistent entry of structured information about the presence of a tardive syndrome, its severity, and its associated degree of disability. Nevertheless, in combination with rating scale data (e.g., AIMS), electronic decision support could help identify individuals with a tardive syndrome who may benefit from a trial of a VMAT2 inhibitor. Information from laboratory data, diagnoses, or problem lists would also be helpful to incorporate in terms of potential contraindications to VMAT2 inhibitor treatment (i.e., tetrabenazine and deutetrabenazine are contraindicated in the presence of hepatic impairment, valbenazine is not recommended for use in individuals with severe renal impairment).

Psychosocial Interventions

Statement 15: Coordinated Specialty Care Programs

APA recommends (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.*

Implementation

For individuals with a first episode of psychosis, coordinated specialty care (CSC) 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 research initiative, 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; National Institutes of Mental Health 2019). Similar CSC programs, which are sometimes referred to as team-based, multicomponent interventions, have also 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 often include individuals with diagnoses other than schizophrenia but 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). Programs are also available that are aimed at early identification and treatment of attenuated psychosis syndrome or related syndromes of high psychosis risk (Addington et al. 2017b; Cotton et al. 2016); however, these programs are not within the scope of this guideline recommendation because they include individuals who do not have a psychiatric diagnosis or who have diagnoses other than schizophrenia at later follow-up times (Fusar-Poli et al. 2016; Iorfino et al. 2019).

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

* 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.

guide the establishment of new programs with evidence-based approaches (National Institute of Mental Health 2019; OnTrackNY 2019; RAISE Early Treatment Program 2019). Tools are also available to assess fidelity of CSC programs to intended implementation principles (Addington et al. 2016, 2018; Durbin et al. 2019; Essock and Addington 2018).

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

Benefits

Use of a CSC 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 strength of research evidence).

Harms

The harms of a CSC 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 CSC 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 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. CSC treatment programs are generally viewed positively by patients and they improve a number of patient-oriented outcomes with minimal risk of harms. (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

Other guidelines did not specifically address the use of CSC 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

More patients may benefit from CSC programs in the U.S. than currently receive it. Consequently, state mental health agencies, health plans, and health organizations may wish to implement initiatives to increase the use of a CSC program among individuals with a first episode of psychosis.

This guideline statement would not be appropriate for a performance-based quality measure unless it were tested for feasibility, usability, reliability, and validity. Factors such as geographic variations in

treatment availability would need to be considered in testing any quality measures related to CSC program use. It may also be difficult to determine whether a patient is receiving appropriate CSC services.

Electronic decision support using passive alerts may be able to prompt clinicians to consider referral to a CSC program if the presence of a first-episode of schizophrenia and the patient's history of prior treatment were accurately and consistently entered into the electronic record as structured data. The electronic record could also incorporate reference information on the location and referral processes for CSC treatment programs in the local area.

Statement 16: Cognitive-behavioral Therapy

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

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. 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).³⁹ 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 illness (Turkington et al. 2006), although some initial reduction in symptoms may be needed for optimal participation. It can also be conducted in group as well as in individual formats, either in-person or via web-based delivery platforms. CBTp can also be made available to family members or other persons of support (Turkington and Spencer 2019). Although patient preferences and treatment availability may

* 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.

³⁹ Videos that demonstrate some of the approaches to CBTp are available at: I can feel better: <https://www.icanfeelbetter.org/cbtpskills>. Accessed April 1, 2019.

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 eight weeks to five 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 2013). Although the available research suggests that treatment benefits are no longer significant when assessed more than six 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). However, engagement strategies, such as motivational interviewing, can be useful in helping patients explore whether CBTp might have potential benefits for them that would offset such concerns.

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, supervision in CBTp techniques, and experience in treating individuals with schizophrenia. 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. Stepped care approaches, learning collaborative models, and other approaches to best-practice consultations show promise as ways to enhance delivery of CBTp in community settings (Creed et al. 2014; Kopelovich 2019a, 2019b; Stirman et al. 2010).

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 strength of research evidence). CBTp can also be associated with short-term improvements (e.g., for up to 6 months) in quality of life (low strength of research evidence) and global, social, and occupational function (moderate strength of research evidence).

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 six months after CBTp treatment seemed to outweigh the minimal harms of CBTp treatment. (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

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 may not be appropriate for a performance-based quality measure because of the impact of logistical barriers to CBT including geographic variations in availability of CBTp, and the difficulty in identifying whether delivered psychotherapy is CBT. Reminders about CBT are also not well-suited to incorporation into electronic health record clinical decision support. Anecdotal observations suggest that use of CBTp is infrequent in the U.S. (Kopelovich et al. 2019b). Consequently, health organizations and health plans may wish to implement programs to increase the use of CBTp among individuals with schizophrenia.

Statement 17: Psychoeducation

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

* 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

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 2016a). In addition, 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 Merinder 2002). 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 (Bäumli et al. 2006). Teaching of illness management or self-management strategies (Substance Abuse and Mental Health Services Administration 2010a), as discussed in Statement 21, is often incorporated into psychoeducation. 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. Information that may be useful to patients and families as a part of psychoeducation is available through SMI Adviser (<https://smiadviser.org/>).

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 strength of research evidence) and reductions in relapse rates (moderate strength of research evidence). 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 strength of research evidence).

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 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

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 may not be appropriate for a performance-based quality measure because of the diversity of psychoeducational approaches and services, and uncertainty regarding linking specific patient needs for psychoeducation with markers of delivery of 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 18: Supported Employment Services

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 (Becker and Drake 2003; Frederick and VanderWeele 2019; Substance Abuse and Mental Health Services Administration 2010b). 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

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Dixon 2014). For individuals whose goals are related to educational advancement prior to pursuit of employment, supported educational services may also be pursued (Substance Abuse and Mental Health Services Administration 2012b).

Of approaches to supported employment, the bulk of studies involve individual placement and support (IPS) (Becker and Drake 2003; Frederick and VanderWeele 2019; McDonagh et al. 2017; Substance Abuse and Mental Health Services Administration 2010b). In addition to a focus on rapid attainment of competitive employment, IPS emphasizes patient preferences in the types of jobs sought, the nature of the services that are delivered, and the outreach that occurs with potential employers (Marino and Dixon 2014). Patient preferences also guide whether to disclose the presence of a psychiatric illness to the employer with over half of individuals choosing to disclose this information (DeTore et al. 2019). Services are offered to anyone who is interested with no exclusion criteria for participation. 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 employment (McDowell and Fossey 2015). 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. In addition to job-related benefits of supported employment, there is some evidence of modest reductions in symptoms and a reduced risk of hospitalization associated with obtaining a job (Bouwmans et al. 2015; Burns et al. 2007; Charzyńska et al. 2015; Hoffmann et al. 2014; Luciano et al. 2014).

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). Even when individuals do not experience initial success with supported employment, addition of cognitive remediation may improve vocational outcomes (McGurk et al. 2015, 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). Although data is limited, 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 (Kirsh 2016) and being unaware that some individuals with schizophrenia are able to function at high levels of occupational achievement (Cohen et al. 2017). In addition, concerns about losing disability benefits or health insurance may lead some individuals to forego supported employment opportunities (Kirsh 2016). Such concerns are not entirely unrealistic because many of the competitive jobs that individuals do obtain are entry-level and/or part-time positions without health insurance benefits (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.

For clinicians and organizations that wish to learn more about supported employment or develop supported employment programs, additional information is available through SMI Adviser (<https://smiadviser.org/>), Navigate (<https://navigateconsultants.org/manuals/>), and the Boston University Center for Psychiatric Rehabilitation (<https://cpr.bu.edu/>).

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 strength of research evidence), 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 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

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 may not be appropriate for a performance-based quality measure because of the barriers to supported employment including variations in availability, and difficulty identifying when patients desire competitive employment. 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 19: Assertive Community Treatment

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 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

* 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 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. 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). 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. For these reasons, ACT is often used in individuals who have a history of poor engagement with services leading to frequent relapse or social disruption (e.g., homelessness; legal difficulties, including imprisonment), although it can also be used for individuals who are better engaged but still have high rates of service utilization. Many individuals who are referred for ACT are also at risk for poor adherence and may benefit from consideration of a long-acting injectable antipsychotic medication. (See Guideline Statement 10.)

Studies of ACT suggest that it is associated with comparable symptom improvement to other treatment delivery approaches and 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 strength of research evidence).

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, patients may be reluctant to accept ACT services because of impaired awareness of a need for treatment. In this context, ACT may be used as one component of court-mandated care (e.g., assisted outpatient treatment, community treatment order, outpatient commitment). 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 19.)

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 may not be appropriate for a performance-based quality measure because of the impact of logistical barriers to ACT including geographic variations in availability. Reminders about ACT are also well-suited to incorporation into electronic health record clinical decision support because of the multiple patient-specific factors that may contribute to a decision to recommend ACT. 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 20: Family Interventions

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, person(s) of support, 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 plan for and access help in a crisis. Other goals include helping individuals repair or strengthen their connections with family members and other members of their support system.

Family interventions are systematically delivered, extend beyond conveying of information, and focus on the future rather than on past events (Mueser et al. 2013). The family interventions that are suggested in this guideline statement go beyond the basics of family involvement and illness education that are important for good clinical care. They may include structured approaches to problem solving, training in how to cope with illness symptoms, assistance with improving family communication, provision of emotional support, and strategies for reducing stress and enhancing social support networks (McDonagh et al. 2017; McFarlane 2016; Mueser et al. 2013). Family interventions can be particularly important early in the course of schizophrenia (McFarlane 2016) but can also be helpful during any phase of treatment.

Most patients want family to be involved in their treatment (Cohen et al. 2013). Nevertheless, even when a patient does not wish for 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 2016a). Although some health professionals may be unsure about legal or regulatory aspects of sharing information, general information that is not 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). 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) (U.S. 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

* 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.

emergency circumstances (U.S. Department of Health and Human Services; Office for Civil Rights 2017b).

The family interventions that have been studied include a variety of formats and approaches (McDonagh et al. 2017; McFarlane 2016). Interventions may or may not include the patient and can be conducted with a single family or a multi-family group. In many early studies, family interventions included the patient and were led by a member of the patient's clinical care team. This approach allowed a liaison to develop among the care team, the patient, members of the family, and other person(s) of support. Other studies have been conducted independent of the patient's care team. 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). Given the diversity of options for family interventions, the selection of a specific approach 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. 2017a). Evidence suggests that benefits of family interventions are greatest when more than 10 treatment sessions are delivered over a period of at least seven 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 two to three hours each (Dixon et al. 2011; Lucksted et al. 2013; Marcus et al. 2013; Toohy et al. 2016).

A common barrier to implementing family interventions relates to program availability. However, guidance is available on developing family intervention programs focused on psychoeducation (Glynn et al. 2014; Substance Abuse and Mental Health Services Administration 2009). In addition, 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 strength of research evidence) and reduce core illness symptoms (low strength of research evidence).

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 20.)

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 and felt that it would be preferable for the guideline statement to make specific mention of other persons of support who may be involved with the patient and are commonly included in such interventions 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 21: Self-management Skills and Recovery-focused Interventions

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 seven 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. 2010; 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, psychoeducation, and peer-based interventions 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 peer-based interventions are limited (Castelein et al. 2015; Chien et al. 2019) and studies of recovery-focused interventions have also been small in number. Nevertheless, the available information suggests that these interventions may promote increased recovery, hope, and empowerment among individuals with serious mental illnesses (Le Boutillier et al. 2011; Mueser et al. 2013; 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 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 2010a). Other resources are also available through the Boston University Center for Psychiatric Rehabilitation (<https://cpr.bu.edu/>), the Center on Integrated Health Care and Self-

* 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.

Directed Recovery (<https://www.center4healthandsdc.org/>), Digital Opportunities for Outcomes in Recovery Services (<https://www.digitalpsych.org/project/digital-opportunities-for-outcomes-in-recovery-services>), Mental Health America (<https://www.mhanational.org/self-help-tools>), the National Alliance on Mental Illness (<https://www.nami.org/>), Navigate (<https://navigateconsultants.org/manuals/>), SMI Adviser (<https://smiadviser.org/individuals-families>), and the Temple University Collaborative on Community Inclusion (<http://www.tucollaborative.org/>).

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 strength of research evidence). 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 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

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 22: Cognitive Remediation

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 particular strategies can be used that bypass specific cognitive limitations. Some programs add aspects of social and communication skills to neurocognitive elements of remediation (Pentarakaki 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 in individuals with schizophrenia at least on a short-term basis (Harvey et al. 2018; McDonagh et al. 2017; Revell et al. 2015). Although long-term follow-up studies of cognitive remediation are not available in individuals with schizophrenia, data from healthy older individuals show long-term improvements as a result of cognitive training (Rebok et al. 2014). Beneficial effects on psychosocial outcomes seem particularly robust when cognitive remediation is used as a component of or adjunct to other forms of psychiatric rehabilitation rather than being delivered as a stand-alone intervention (McGurk et al. 2007; Revell et al. 2015; van Duin et al. 2019; Wykes et al. 2011). 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 cognitive 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). In addition, web-based programs have been used in clinical trials and may provide options for patients without access to in person cognitive remediation programs (Jahshan et al. 2019; Kukla 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 moderate improvements in specific aspects of cognition (Harvey et al. 2018; Wykes et al. 2011) as well as small positive effects on social, occupational, and global function, core illness symptoms (low strength of research evidence), and negative symptoms

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(moderate strength of research evidence) 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 22.)

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 23: Social Skills Training

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

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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 includes homework assignments to facilitate skill acquisition. Other 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, group sessions are augmented with video or technologically-based interventions, in vivo community trips to practice social skills (Glynn et al. 2002; Mueser et al. 2010), and involvement of support people who were accessible, pleasant, and knowledgeable about the local environments' resources and limitations (Mueser et al. 2010; Tauber et al. 2000).

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 (Bellack and Goldberg 2019; Bellack 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 strength of research evidence).

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 strength of research evidence 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.

Statement 24: Supportive Psychotherapy

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). Because the evidence related to its benefits is limited, supportive psychotherapy should not take precedence over other evidence-based psychosocial treatments (e.g., coordinated specialty care, CBTp, psychoeducation). When compared to treatment as usual, no advantage was seen for supportive psychotherapy in terms of global or social function (Buckley et al. 2015; McDonagh et al. 2017); however, these findings 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

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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 strength of research evidence). 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.

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 24.)

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 interventions 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.

Undergoing Copyediting

Areas for Further Research in Individuals with Schizophrenia

Overall:

- Improve the 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
- Increase collection of data on patient-centered outcomes (e.g., quality of life, social functioning, physical health, recovery)
- Improve systematic collection of information on harms, including in studies of psychosocial interventions
- Identify approaches (e.g., pharmacogenomics, biomarkers, symptom clusters, and other predictive variables) for optimizing treatment selection
- Determine efficient, valid, and reliable approaches to quantitative measurement of positive symptoms, negative symptoms, functioning, quality of life, and treatment related side effects
- Determine ways in which demographic or sociocultural factors influence treatment outcomes
- Determine the durability of treatment effects and potential for long-term harms through long-term studies (e.g., at least one year of treatment with follow-up assessments at three to five years)
- Determine the benefits, harms and appropriate use 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)
- Identify methods that will allow information from mobile technologies, "wearables" and "big data" to inform assessment, treatment, and future research
- Determine optimal monitoring frequencies and approaches to detect treatment related benefits and side effects
- Identify optimal approaches to improving physical health in individuals with schizophrenia
- Identify optimal approaches to treatment of co-occurring substance use disorders in individuals with schizophrenia
- Identify approaches to redesign workflows and models of care delivery to improve the use of best practices in the treatment of schizophrenia
- Identify approaches to determine the optimal setting of care (e.g., inpatient, partial hospital, intensive outpatient, psychosocial rehabilitation, Clubhouse models)
- Identify optimal approaches to integrate recovery based and peer-based programs into other models of care delivery

- Identify optimal approaches to care coordination and case management, including intensive case management

Medications and other somatic interventions

- Determine the comparative effectiveness of newer SGAs (including LAIs, comparisons with some FGAs and use of comparable dosing strategies)
- Determine the comparative harms of antipsychotic medications including long-term harms and rare but serious harms
- Determine optimal antipsychotic treatment approaches for individuals with suicidal or aggressive behaviors, including additional studies of clozapine for aggressive behavior
- Identify risks and benefits of using other medications (e.g., lithium, anticonvulsants, antidepressants, stimulants, benzodiazepines, other sedative-hypnotics) in combination with antipsychotic medications to address specific target symptoms or treatment non-response
- Identify risks and benefits of concomitant use of more than one antipsychotic medication
- Identify 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
- Determine optimal approaches to making medication changes (i.e., switching from one antipsychotic to another) to minimize risk of relapse and reduce potential for treatment-related side effects
- Identify optimal clinical approaches for determining when a treatment trial is adequate and when treatment resistance is present
- Determine relationships between blood levels of antipsychotic medications (including active metabolites) and therapeutic response that can be used to guide dose titration and determination of treatment adequacy
- Identify whether there are subgroups of patients for whom medication discontinuation may be possible
- Determine whether intermittent treatment or early relapse is associated with increased long-term harms (e.g., greater treatment resistance, neurobiological changes)
- Determine optimal approaches to prevention and treatment of specific side effects of antipsychotic medications including neurological side effects, weight gain, diabetes, metabolic syndrome, and cardiovascular disease
- Determine the optimal duration of treatments for neurological side effects (e.g., VMAT2 inhibitors for tardive dyskinesia, anticholinergic agents for parkinsonism).
- Determine the efficacy and comparative effectiveness of neurostimulation approaches (e.g., ECT, TMS) in conjunction with other treatments for schizophrenia

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

- Conduct 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
- Develop methods to study psychosocial interventions to identify key contributors to benefit (e.g., clinician experience, treatment fidelity, use of shared decision-making, clinician-patient alliance, family engagement, setting of care)
- Investigate the benefits and harms of other psychosocial interventions (e.g., mindfulness, acceptance and commitment therapy, metacognitive reflection and insight therapy, Open Dialogue, exercise, music and dance therapies)
- Determine benefits, harms and optimal approaches for implementation of peer-based services, recovery-oriented programs and self-management strategies
- Determine the components of multi-component interventions (e.g., CSC) that are crucial to positive outcomes
- Determine whether the effectiveness and sustainability of CSC with longer term program participation
- Determine the elements of supported employment programs that are most likely to foster long-term competitive employment

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.F.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. National Alliance on Mental Illness, Mental Health America, and Schizophrenia and Related Disorders Alliance of America 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, 2017c; 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; Horvitz-Lennon et al. 2009).

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 Institute 2011; Fernandes-Taylor and Harris 2012; Iyer et al. 2016; Pincus et al. 2016; Watkins et al. 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; Greenhalgh et al. 2004; Horvitz-Lennon et al. 2009). When performance is compared among 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 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. 98 individuals and 20 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.

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. In terms of the Neuroscience-based Nomenclature (<http://www.nbn2.org/>), these medications are categorized as D2 receptor antagonist (fluphenazine, haloperidol, perphenazine, pimozide); D2 and 5-HT2 receptor antagonist (chlorpromazine, iloperidone, loxapine, lurasidone, olanzapine, thioridazine, trifluoperazine, ziprasidone); D2 and 5-HT1A receptor partial agonist and 5-HT2A receptor antagonist (aripiprazole, brexpiprazole); a 5-HT2, D2 and NE alpha-2 receptor antagonist (asenapine); a D2, 5-HT2 and NE alpha-2 receptor antagonist (clozapine, paliperidone, risperidone); and a D2 and 5-HT2 receptor antagonist and NET reuptake inhibitor (quetiapine). Within each group of antipsychotic medications, there is significant variability in the pharmacological properties 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 2016a).

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 individualized 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”). (Adapted from DSM-5)

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. (Adapted from DSM-5)

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; U.S. 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.

I² 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 2016a).

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). (Adapted from DSM-5.)

Over-the-counter medications or supplements Drugs or supplements that can be bought without a prescription.

Person-centered care Person-centered care, sometimes referred to as patient-centered care, is care that is respectful of and responsive to individual preferences, needs, and values and ensures that an individual's values guide all clinical decisions (Institute of Medicine 2001). In person-centered care, patients, families, and other persons of support are provided with information that allows them to make informed decisions (Institute of Medicine 2006). Evidence-based interventions should be adapted to meet individual needs and preferences where possible (van Dulmen et al. 2015) and shared decision-making and self-management approaches are encouraged (Institute of Medicine 2006). Person-centered care is achieved through a dynamic and collaborative relationship among individuals, families, other persons of support, and treating clinicians that supports the individual's realistic health and life goals and informs decision-making to the extent that the individual desires (American Geriatrics Society Expert Panel on Person-Centered Care 2016).

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).

Treatment as usual Treatment that is consistent with care received for a specific condition in a real-world non-research context. Treatment as usual, sometimes referred to as usual care or standard care, is often used as an active comparison condition for studies of new interventions. Elements of treatment as usual are heterogenous and differ with each study, but can include medication treatment, medication management, case management, rehabilitation services, and psychotherapy (McDonagh et al. 2017).

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Zyprexa (olanzapine) [product monograph]. Toronto, Ontario, Canada, Eli Lilly Canada Inc, April 2018b

Zyprexa Relprevv (olanzapine) [prescribing information]. Indianapolis, IN, Eli Lilly and Co, March 2018

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

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APA Council on Psychiatry and the Law, Subcommittee on Correctional Psychiatry	Schizophrenia International Research Society
Academy of Consultation-Liaison Psychiatry	Treatment Advocacy Center Psychiatric Advisory Board
Alkermes, Inc.	World Psychiatric Association Section on Schizophrenia
American Academy of Child and Adolescent Psychiatry	
American Psychological Association	

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)

	Systematic reviews	Number of publications	Number of trials in systematic reviews	Number of subjects in systematic reviews	Number of additional trials	Number of publications	Number of subjects in additional trials	Total Number of subjects
FGA vs. SGA	1	2	111	118,503	5	7	1,055	119,558
SGA vs. SGA	1	1	138	47,189	24	28	6,672	53,861
Assertive community treatment	1	1	14	2,281	1	1	118	2,399
Cognitive adaptive training	0	0	0	0	3	4	290	290
Cognitive behavioral therapy	3	3	89	7,154	5	6	823	7,977
Cognitive remediation	2	2	57	2,885	4	5	341	3,226
Early intervention for first-episode psychosis	0	0	0	0	4	9	2,363	2,363
Family interventions	1	1	27	2,297	6	8	562	2,859
Intensive case management	1	1	10	1,652	1	1	77	1,729
Interventions for schizophrenia and co-occurring SUD	1	1	32	3,165	0	0	0	3,165
Illness self-management	1	1	13	1,404	1	1	210	1,614
Psychoeducation	1	1	10	1,125	0	0	0	1,125
Social skills training	0	0	0	0	3	4	433	433
Supported employment	1	1	14	2,265	2	3	1477	3,742
Supportive psychotherapy	1	1	5	822	0	0	0	822

Abbreviations: FGA=first-generation antipsychotic; SGA=second-generation antipsychotic

Treatment of Neurological Side Effects of Antipsychotic Medications

Additional searches were undertaken to supplement the AHRQ review and to identify studies that addressed approaches to treatment of neurological side effects of antipsychotic medications. Search strategies for MEDLINE (PubMed) and Cochrane Library are shown in Tables 2 and 3, respectively. For each search, all available citations were identified from the inception of the database to July 29, 2018 when the searches were conducted. A search of MEDLINE (PubMed) yielded 2980 citations and a search of the Cochrane Library yielded 2450. After duplicate citations were removed, titles and abstracts for 4196 articles were screened by one reviewer (L.J.F.) to identify articles in humans 18 years of age or

older, published in English, that investigated the treatment of antipsychotic associated dystonia, 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

#1	Search "Akineton"[TIAB] OR "Amantadine"[MH] OR "Amantadine"[TIAB] OR "Artane"[TIAB] OR "Atropine"[MH] OR "Atropine"[TIAB] OR "Benadryl"[TIAB] OR "Benztropine"[MH] OR "Benztropine"[TIAB] OR "Biperiden"[MH] OR "Biperiden"[TIAB] OR "Bromocriptine"[MH] OR "bromocriptine"[TIAB] OR "Cogentin"[TIAB] OR "Cuvposa"[TIAB] OR "Dantrium"[TIAB] OR "Dantrolene"[MH] OR "Dantrolene"[TIAB] OR "Diphenhydramine"[MH] OR "Diphenhydramine"[TIAB] OR "Glycopyrrolate"[MH] OR "Glycopyrrolate"[TIAB] OR "Nitoman"[TIAB] OR "Procyclidine"[MH] OR "Procyclidine"[TIAB] OR "Robinul"[TIAB] OR "Symmetrel"[TIAB] OR "Tetrabenazine"[MH] OR "Tetrabenazine"[TIAB] OR "Trihexyphenidyl"[MH] OR "Trihexyphenidyl"[TIAB] OR "Xenazine"[TIAB] OR "beta blocker"[TIAB] OR "beta blockers"[TIAB] OR "beta adrenergic antagonist"[TIAB] OR "beta adrenergic antagonists"[TIAB] OR "beta adrenergic blocking"[TIAB] OR "beta adrenergic blocking agent"[TIAB] OR "beta adrenergic blocking agents"[TIAB] OR "adrenergic beta antagonists"[TIAB] OR "propranolol"[TIAB] OR "pindolol"[TIAB] OR "atenolol"[TIAB] OR "inderal"[TIAB] OR "muscarinic antagonists"[MeSH Terms] OR "adrenergic beta antagonists"[MeSH Terms] OR "amantadine"[MeSH Terms] OR "benztropine"[MeSH Terms] OR "diphenhydramine"[MeSH Terms] OR "trihexyphenidyl"[MeSH Terms] OR "propranolol"[MeSH Terms] OR "pindolol"[MeSH Terms] OR "atenolol"[MeSH Terms]	163354
#2	Search "9-hydroxy-risperidone"[TIAB] OR "abilify"[TIAB] OR "antipsychotic agents"[MeSH Major Topic] OR "antipsychotic agents"[MeSH Terms] OR "antipsychotic"[TIAB] OR "antipsychotics"[TIAB] OR "aripiprazole"[NM] OR "aripiprazole"[TIAB] OR "Asenapine"[NM] OR "Asenapine"[TIAB] OR "Chlorpromazine"[MH] OR "Chlorpromazine"[NM] OR "Chlorpromazine"[TIAB] OR "Chlorprothixene"[MH] OR "Chlorprothixene"[NM] OR "Chlorprothixene"[TIAB] OR "Clopixol"[TIAB] OR "Clozapine"[MH] OR "clozapine"[NM] OR "clozapine"[TIAB] OR "clozariil"[TIAB] OR "Consta"[TIAB] OR "Droperidol"[MH] OR "droperidol"[NM] OR "droperidol"[TIAB] OR "Fanapt"[TIAB] OR "Fazaclol"[TIAB] OR "Fluanxol"[TIAB] OR "flupenthixol"[NM] OR "flupenthixol"[TIAB] OR "flupenthixol"[TIAB] OR "fluphenazine depot"[NM]	113808

	<p>OR "fluphenazine depot"[TIAB] OR "fluphenazine enanthate"[NM] OR "fluphenazine enanthate"[TIAB] OR "Fluphenazine"[MH] OR "Fluphenazine"[TIAB] OR "Geodon"[TIAB] OR "Haldol"[TIAB] OR "haloperidol decanoate"[NM] OR "haloperidol decanoate"[TIAB] OR "Haloperidol"[MH] OR "haloperidol"[NM] OR "haloperidol"[TIAB] OR "lloperidone"[TIAB] OR "Inapsine"[TIAB] OR "Invega"[TIAB] OR "Largactil"[TIAB] OR "Loxapac"[TIAB] OR "Loxapine"[MH] OR "Loxapine"[NM] OR "Loxapine"[TIAB] OR "Loxitane"[TIAB] OR "Lurasidone"[TIAB] OR "Mellaril"[TIAB] OR "Mesoridazine"[MH] OR "Mesoridazine"[NM] OR "Mesoridazine"[TIAB] OR "Moban"[TIAB] OR "Modecate"[TIAB] OR "Molindone"[MH] OR "Molindone"[NM] OR "Molindone"[TIAB] OR "Navane"[TIAB] OR "olanzapine"[NM] OR "olanzapine"[TIAB] OR "Orap"[TIAB] OR "paliperidone palmitate"[NM] OR "Perphenazine"[MH] OR "Paliperidone"[TIAB] OR "Perphenazine"[NM] OR "Perphenazine"[TIAB] OR "Pimozide"[MH] OR "Pimozide"[NM] OR "Pimozide"[TIAB] OR "Prolixin"[TIAB] OR "quetiapine"[TIAB] OR "Relprevv"[TIAB] OR "Risperdal"[TIAB] OR "Risperidone"[MH] OR "Risperidone"[NM] OR "Risperidone"[TIAB] OR "Saphris"[TIAB] OR "Serentil"[TIAB] OR "Seroquel"[TIAB] OR "Stelazine"[TIAB] OR "Sustenna"[TIAB] OR "Symbyax"[TIAB] OR "Taractan"[TIAB] OR "Thioridazine"[MH] OR "Thioridazine"[NM] OR "Thioridazine"[TIAB] OR "Thiothixene"[MH] OR "Thiothixene"[NM] OR "Thiothixene"[TIAB] OR "Thorazine"[TIAB] OR "Trifluoperazine"[MH] OR "Trifluoperazine"[NM] OR "Trifluoperazine"[TIAB] OR "Trilafon"[TIAB] OR "Zeldox"[TIAB] OR "ziprasidone"[NM] OR "ziprasidone"[TIAB] OR "zuclopenthixol"[TIAB] OR "Zydis"[TIAB] OR "Zyprexa"[TIAB]</p>	
#3	<p>Search "akathisia"[TIAB] OR "Akathisia, Drug-Induced"[MH] OR "drug induced parkinsonism"[TIAB] OR "Dyskinesia, Drug-Induced"[MH] OR "dystonic reaction"[TIAB] OR "dystonic reactions"[TIAB] OR "extrapyramidal reactions"[TIAB] OR "extrapyramidal side effect"[TIAB] OR "extrapyramidal side effects"[TIAB] OR "extrapyramidal signs"[TIAB] OR "extrapyramidal syndrome"[TIAB] OR "extrapyramidal syndromes"[TIAB] OR "Neuroleptic Malignant Syndrome"[MH] OR "neuroleptic malignant"[TIAB] OR "tardive dyskinesia"[TIAB] OR "tardive dystonia"[TIAB] OR "neuroleptic induced parkinsonism"[TIAB] OR "medication induced parkinsonism"[TIAB] OR "tardive akathisia"[TIAB]</p>	16341
#4	<p>Search (("animals"[MeSH Major Topic] OR "animals"[MeSH Terms] OR "animal"[TIAB] OR "animals"[TIAB] OR "rat"[TIAB] OR "mouse"[TIAB] OR "mice"[TIAB] OR "rodent"[TIAB] OR "rodents"[TIAB] OR "rats"[TIAB]) NOT ("humans"[MAJR] OR "humans"[MH] OR "human"[TIAB] OR "humans"[TIAB]))</p>	4437558

#5	Search "meta analysis"[TIAB] OR "meta analyses"[TIAB] OR "meta analytic"[TIAB] OR "metaanalysis"[TIAB] OR "metaanalysis"[TIAB] OR "systematic review"[TIAB] OR "systematic reviews"[TIAB] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[PT] OR "randomised"[TIAB] OR "randomized"[TIAB] OR "randomisation"[TIAB] OR "randomization"[TIAB] OR "randomly"[TIAB] OR "placebo"[TIAB] OR "sham"[TIAB] OR "trial"[TIAB] OR "groups"[TIAB]	2841422
#6	Search "controlled clinical trial"[PT] OR "blinded" [TIAB] OR "case control" [TIAB] OR "clinical trial" [TIAB] OR "clinical trials" [TIAB] OR "Cohort Analysis" [TIAB] OR "cohort research" [TIAB] OR "cohort study" [TIAB] OR "cohort trial" [TIAB] OR "comparator group" [TIAB] OR "controlled studies" [TIAB] OR "controlled study" [TIAB] OR "controlled trial" [TIAB] OR "controlled trials" [TIAB] OR "double blind" [TIAB] OR "followup study" [TIAB] OR "longitudinal research" [TIAB] OR "longitudinal study" [TIAB] OR "longitudinal trial" [TIAB] OR "multicenter trial" [TIAB] OR "multicenter trials" [TIAB] OR "naturalistic research" [TIAB] OR "naturalistic study" [TIAB] OR "naturalistic trial" [TIAB] OR "prospective cohort" [TIAB] OR "prospective research" [TIAB] OR "prospective study" [TIAB] OR "prospective trial" [TIAB] OR "retrospective cohort" [TIAB] OR "retrospective research" [TIAB] OR "retrospective study" [TIAB] OR "retrospective trial" [TIAB] OR "single blind" [TIAB]	1513299
#7	Search (#1 AND #2) OR (#1 AND #3) OR (#2 AND #3)	15146
#8	Search #7 NOT #4	11508
#9	Search #8 AND (#5 OR #6)	3156
#10	Search "english"[Language] AND #9	2980

Table B-3. Strategy for Cochrane Library search on treatments for neurological side effects of antipsychotic medications

ID	Search	Hits
#1	"Akineton" or "Amantadine" or "Artane" or "Atropine" or "Benadryl" or "Benztropine" or "Biperiden" or "bromocriptine" or "Cogentin" or "Dantrium" or "Dantrolene" or "Diphenhydramine" or "Glycopyrrolate" or "Procyclidine" or "Robinul" or "Symmetrel" or "Tetrabenazine" or "Trihexyphenidyl" or "Xenazine" or "beta blocker" or "beta blockers" or "beta adrenergic antagonist" or "beta adrenergic antagonists" or "beta adrenergic blocking" or "beta adrenergic blocking agent" or "beta adrenergic blocking agents" or "adrenergic beta antagonists" or "propranolol" or "pindolol" or "atenolol" or "inderal":ti,ab,kw (Word variations have been searched)	21056

#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 "Fazaclo" or "Fluanxol" or "flupenthixol" or "flupenthixol" or "fluphenazine depot" or "fluphenazine enanthate" or "Fluphenazine" or "Geodon" or "Haldol" or "haloperidol decanoate" or "haloperidol" or "Iloperidone" 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 "Zeldox" or "ziprasidone" or "zuclopenthixol" or "Zydis" or "Zyprexa"	16885
#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"	2505
#4	(#1 and #2) or (#1 and #3) or (#2 and #3)	2473
	Limited to Cochrane Reviews, Other Reviews and Trials	2450

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 medication-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 Determination of Treatment Plan

Statement 1: Assessment of Possible Schizophrenia

APA recommends (1C) that the initial assessment of a patient with a possible psychotic disorder include the reason the individual is presenting for evaluation, the patient's goals and preferences for treatment, a review of psychiatric symptoms and trauma history, an assessment of tobacco use and other substance use, a psychiatric treatment history, an assessment of physical health, an assessment of psychosocial and cultural factors, a mental status examination including cognitive assessment, and an assessment of risk of suicide and aggressive behaviors, as outlined in APA's Practice Guidelines for the Psychiatric Evaluation of Adults (3rd edition).

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*, 3rd edition (American Psychiatric Association 2016a). 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.

Grading of the Overall Supporting Body of Research Evidence for Assessment of Possible Schizophrenia Based on the limitations of the evidence for assessment of possible schizophrenia, no grading of the body of research evidence is possible.

Statement 2: Use of Quantitative Measures

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

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*, 3rd edition (American Psychiatric Association 2016a).

Grading of the Overall Supporting Body of Research Evidence for Use of Quantitative Measures Based on the limitations of the evidence for use of quantitative measures, no grading of the body of research evidence is possible.

Statement 3: Evidence-based Treatment Planning

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.

Grading of the Overall Supporting Body of Research Evidence for Evidence-based Treatment Planning
Based on the limitations of the evidence for evidence-based treatment planning, no grading of the body of research evidence is possible.

Pharmacotherapy

Statement 4: Antipsychotic Medications

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 RCTs of antipsychotic medications in schizophrenia (Huhn et al. 2019; Leucht et al. 2017). 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 research evidence 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),

* 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.

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 six 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.

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

	Number of studies	Number of subjects	Measure	95% CI	I ²	Comments
All studies	105	22,741	Mean effect size=0.47	0.42, 0.51	52%	
Any response with drug vs. placebo	97	20,690	Response ratio=1.93	1.72, 2.19		NNT=6
Good response	30	8,408	Response ratio=1.96	1.65, 2.44		NNT=8; 23% good response with antipsychotic vs. 14% with placebo
At least minimal response	46	8,918	Response ratio=1.75	1.59, 1.07		NNT=5; 51% minimal response with antipsychotic vs. 30% with placebo
Discontinuation for any reason	105	22,851	Risk ratio=1.25	1.20, 1.31		NNT=11; 38% discontinuation with antipsychotic vs. 56% with placebo
Discontinuation for inefficacy	94	23,017	Risk ratio=2.09	1.90, 2.32		NNT=7; 13% discontinuation with antipsychotic vs. 26% with placebo
Positive symptoms	64	18,174	SMD=0.45	0.40, 0.50	56%	
Negative symptoms	69	18,632	SMD=0.35	0.31, 0.40	42%	
Depression	33	9,658	SMD=0.27	0.20, 0.34	50%	
Quality of life	6	1,900	SMD=0.35	0.16, 0.51	43%	
Social functioning	10	3,077	SMD=0.34	0.21, 0.47	46%	
Use of antiparkinsonian medications	63	14,942	Risk ratio=1.93	1.65, 2.29		NNH=12; 19% with antipsychotic vs. 10% with placebo
Sedation	86	18,574	Risk ratio=2.80	2.30, 3.55	54%	14% with antipsychotic vs. 6% with placebo
Weight gain	59	15,219	SMD=-0.43	-0.55, -0.30	73%	
Prolactin increase	51	15,219	SMD=-0.43	-0.55, -0.30	91%	
QTc prolongation	29	9,833	SMD=-0.19	-0.29, -0.08	80%	

Abbreviations: CI=confidence interval; NNH=number needed to harm; NNT=number needed to treat; QTc=corrected QT interval; SMD=standardized mean difference,

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; $I^2=54%$; 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 (MD) 3.24, 95% CI 1.62 to 4.86) and olanzapine (15 RCTs, N=4,209; MD 2.31, 95% CI 0.44 to 4.18) were associated with greater improvements in total 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).

In an additional network meta-analysis of 32 antipsychotic medications, Huhn and colleagues (Huhn et al. 2019) included 402 placebo-controlled and head-to-head randomized controlled trials that included a total of 53,463 adult participants with acute symptoms and a diagnosis of schizophrenia or a related disorder. Studies that focused on individuals with a first-episode of psychosis or treatment resistance were not included as were studies in which individuals had concomitant medical illnesses or a predominance of negative or depressive symptoms. For the majority of antipsychotics, treatment was associated with a statistically significant reduction in overall symptoms as compared to placebo and there were few significant differences between individual drugs. With antipsychotic medications that did not differ significantly from placebo, there were numerical differences favoring the antipsychotic medication and the number of subjects in the network meta-analysis was small, yielding a wide credible interval (CrI). Only clozapine, amisulpride, zotepine, olanzapine, and risperidone exhibited greater efficacy than many other antipsychotic medications for overall symptoms with the greatest benefit noted with clozapine (SMD -0.89, 95% CrI -1.08 to -0.71). Discontinuation rates for inefficacy paralleled the findings for treatment efficacy. In terms of positive symptoms, negative symptoms and depressive symptoms, the majority of the medications showed a statistically significant difference from placebo, with the exception of several antipsychotic agents for which sample sizes were small and CrIs were wide. Few studies had assessed effects of antipsychotic medications on social functioning. As in the Leucht and colleagues (Leucht et al. 2017) meta-analysis, side effect profiles differed considerably among the antipsychotic medications.

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).

In terms of dose response effects on antipsychotic medication effectiveness, standard doses of antipsychotic medications are superior to low or very low dose treatment in reducing the risk of relapse (Uchida et al. 2011a). In addition, there is evidence of a dose-response relationship for many antipsychotic medications in short-term trials of acute efficacy (Davis and Chen 2004).

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 0.34 to 0.94); 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 and head-to-head comparison data was not available for all available antipsychotic medications. 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; $I^2=0\%$), olanzapine (24 RCTs, N=5,708; RR 1.89, 95% 1.57 to 2.27; $I^2=0\%$), risperidone (25 RCTs, N=4,581; RR 1.32, 95% CI 1.09 to 1.60; $I^2=0\%$), and ziprasidone (seven RCTs, N=1,597; RR 1.68, 95% 1.26 to 2.23; $I^2=0\%$).

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; $I^2=0\%$), risperidone (eight RCTs, N=1313; RR 1.20, 95% CI 1.01 to 1.42; $I^2=84\%$), and ziprasidone (six RCTs, N=1,448; RR 1.13, 95% CI 1.03 to 1.23;

$I^2=31\%$). 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 aripiprazole (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; $I^2=0\%$; follow-up of 6 weeks to 3 months) or aripiprazole (pooled OR 2.50, 95% CI 1.32 to 4.76; $I^2=0\%$; 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-analyses of Leucht and colleagues (Leucht et al. 2017) and Huhn and colleagues (Huhn et al. 2019) 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 with the exception of clozapine. 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.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Antipsychotic Medications

- **Magnitude of effect:** *Moderate*. The magnitude of effect varies among individual antipsychotic medications but is moderate overall based on findings from meta-analyses of placebo-controlled trials.
- **Risk of bias:** *Medium*. Studies are RCTs that are summarized in multiple good quality meta-analyses. Although the risk of bias of individual RCTs varies, most have some limitations and, in older trials, reporting of study design features is often incomplete. Among head-to-head comparison trials, some studies are observational trials and associated with a higher risk of bias.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The studies include subjects from countries around the world with the exception of China. The doses of medication used are representative of usual clinical practice.
- **Directness:** *Direct*. Studies measure functioning, quality of life, core illness symptoms, negative symptoms, and response to treatment.
- **Consistency:** *Consistent*. When multiple studies are available that included a given comparison, results are generally consistent. In addition, the overall direction of effects is generally consistent among antipsychotic medications in placebo-controlled trials.
- **Precision:** *Variable*. For many comparisons, particularly when multiple RCTs are available, findings are precise. However, for other comparisons, imprecision is present due to wide confidence intervals that often cross the threshold for a clinically significant benefit of the intervention.
- **Dose-response relationship:** *Present*. There is evidence of a dose-response relationship in acute treatment trials as well as in studies of antipsychotic medications for relapse prevention.
- **Confounding factors:** *Present*. In placebo-controlled trials, effect sizes have decreased over the past 60 years, apparently due to increases in placebo response rates; these trends are likely to confound comparisons of older and newer medications.
- **Publication bias:** *Suspected*. Among placebo-controlled trials, studies with no effect of treatment appear to have had lower rates of publication.
- **Overall strength of research evidence:** *High*. There are a large number of randomized, double-blind, placebo-controlled trials of antipsychotic medication as well a smaller number of head-to-head comparison RCTs. Although many studies have a moderate risk of bias and publication bias appears to be present, there is also consistency in overall study findings and a dose-response relationship is present, strengthening confidence in the conclusions.

Grading of the Overall Supporting Body of Research Evidence for Harms of Antipsychotic Medications

- **Magnitude of effect:** *Small to moderate*. The magnitude of effect for harms of antipsychotic medication differs by drug and by side effect but is small to moderate overall.
- **Risk of bias:** *Medium to High*. Studies are RCTs that are summarized in multiple good quality meta-analyses. Particularly in older clinical trials, side effects tend not to be assessed or reported as systematically as efficacy and effectiveness related outcomes.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The studies include subjects from around the world with the exception of China. The doses of medication used are representative of usual clinical practice.
- **Directness:** *Variable*. Most studies measure overall adverse events and some measure specific adverse effects, each of which is a direct measure. Other studies measure study withdrawal rates due to adverse effects, which is an indirect measure.
- **Consistency:** *Consistent*. In studies that compare the same medication to placebo, side effect related outcomes are generally consistent in their direction and relative degree. Head-to-head comparison data are less consistent.
- **Precision:** *Precise*. Confidence intervals are narrow for comparisons where multiple studies with good sample sizes are available. For comparisons with a small number of studies or small samples, imprecision is present due to wide confidence intervals. Head-to-head comparisons also have imprecision due to outcomes that cross the threshold for clinically significant harms of the intervention.
- **Dose-response relationship:** *Suspected*. There is less systematic information available on dose-response relationships for side effects of antipsychotic medication; however, the available evidence suggests that greater doses are associated with a greater degree of medication-related side effects.
- **Confounding factors:** *Present*. Cohort effects that are present in efficacy and effectiveness studies of antipsychotic medication are also likely to be relevant when assessing harms of antipsychotic medication.
- **Publication bias:** *Suspected*. Among placebo-controlled trials, studies with no effect of treatment appear to have had lower rates of publication.
- **Overall strength of research evidence:** *Moderate*. Available studies are RCTs that are generally of moderate quality and have good sample sizes. Findings are consistent, with narrow confidence intervals for many comparisons, and likely to exhibit a dose-response relationship.

Antipsychotic Medications in First-episode Schizophrenia

In subgroup analyses, the AHRQ review (McDonagh et al. 2017) found that patients experiencing a first episode of schizophrenia did not show significantly differences in response or remission when treated with olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone. Another systematic review (Zhu et al. 2017) in individuals with a first episode of schizophrenia found that amisulpride, olanzapine, ziprasidone, and risperidone reduced overall symptoms more than haloperidol, but the evidence was noted as being of very low to moderate quality and only 13 studies were available to address this clinical question.

Treatment Approaches to Partial Response or Nonresponse

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 five 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). A subsequent systematic review and meta-analysis by Samara and colleagues (Samara et al. 2018) found 10 relevant RCTs, which included a total of 675 participants. Although no clear differences in response were noted between subjects who received the same dose of medication as compared those who received a higher dose, many of the studies had a moderate to high risk of bias. There were also no differences in other outcomes including the proportion of individuals who left the study early due to adverse effects or for any reason.

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. 2019a) 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 (SMD -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).

Statement 5: Continuing Medications

APA recommends (1A) that patients with schizophrenia whose symptoms have improved with an 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.

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, 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 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.

Several meta-analyses have examined mortality related data with antipsychotic treatment. A meta-analysis of studies with follow-up periods of at least one year found that mortality was increased in individuals who did not receive antipsychotic medication as compared to those who were treated with an antipsychotic medication (pooled risk ratio 0.57; 0.46 to 0.76; p < 0.001 based on 22,141 deaths in 715,904 patient years in four cohort studies; Vermeulen et al. 2017). With continuous treatment with clozapine, mortality was found to be lower in long term follow-up (median 5.4 years) as compared to treatment with other antipsychotic medications (mortality rate ratio = 0.56, 95% CI = 0.36-0.85, P-value = .007; based on 1327 deaths in 217691 patient years in 24 studies; Vermeulen et al. 2019).

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. 2019) 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).

Grading of the Overall Supporting Body of Research Evidence for the Efficacy of Continuing Treatment With an Antipsychotic Medication.

- **Magnitude of effect:** *Strong*. The magnitude of effect is strong in terms of lower relapse rates and lower mortality for individuals who received maintenance treatment with antipsychotic medications as compared to discontinuation of antipsychotic medication.
- **Risk of bias:** *Medium*. Studies include RCTs of antipsychotic discontinuation and observational studies using registry data. Although the registry studies have a greater risk of bias than RCTs, they use prospectively collected data and have good observational study designs.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The doses of medication used are representative of usual clinical practice. The observational studies include data from a nationwide registry and have broad generalizability in contrast to RCTs with more restrictive inclusion and exclusion criteria. However, the applicability of registry data from Nordic countries may be reduced by differences in the health care delivery system as compared to the U.S.
- **Directness:** *Direct*. Studies measured relapse rates and mortality.
- **Consistency:** *Consistent*. Findings showing benefits of maintenance antipsychotic treatment are consistent among the different studies and study designs.
- **Precision:** *Variable*. Most meta-analyses have narrow confidence intervals that do not cross the threshold for clinically significant benefit of treatment; however, some studies have wider confidence intervals.
- **Dose-response relationship:** *Not assessed*.
- **Confounding factors:** *Unclear*. It is possible that missing data or cohort related effects may influence the results from multi-year registry databases. For long-term follow-up studies, which are needed to assess long-term effects of antipsychotic medication, loss of individuals to follow-up and changes in treatment over time may also confound data interpretation.
- **Publication bias:** *Not assessed*.
- **Overall strength of research evidence:** *High*. Available studies include RCTs with a moderate risk of bias. These RCTs are complemented by prospective registry studies with very large sample sizes. Confidence intervals for most outcomes are relatively narrow and findings are consistent in showing substantial benefit for continued antipsychotic medication treatment.

Grading of the Overall Supporting Body of Research Evidence for the Harms of Continuing Treatment With an Antipsychotic Medication.

See Appendix C, Statement 4, Grading of the Overall Supporting Body of Research Evidence for Harms of Antipsychotic Medications.

Statement 6: Continuing the Same Medications

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

Evidence in support of this statement includes the evidence described for antipsychotic efficacy (as described in Appendix C, Statement 4) and the evidence for remaining on antipsychotic treatment (as described in Appendix C, 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 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.

Grading of the Overall Supporting Body of Research Evidence for the Efficacy of Continuing the Same Antipsychotic Medication

- **Magnitude of effect:** *Moderate*. Evidence from two RCTs suggests that a change in medication is associated with a moderate risk of earlier treatment discontinuation than continuing on the same medication.
- **Risk of bias:** *Medium*. Studies are RCTs with a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The studies were conducted in the U.S. Doses of medication used are representative of usual clinical practice. The available RCTs

examine changes in medication aimed at reducing metabolic effects of treatment and a change from a high metabolic risk medication to a low metabolic risk medication may not be representative of other medication changes.

- **Directness:** *Indirect.* Studies measure all-cause treatment discontinuation, which combines effects due to inefficacy and lack of tolerability.
- **Consistency:** *Consistent.* The two studies are consistent in showing benefits of continuing with the same antipsychotic medication.
- **Precision:** *Precise.* Confidence intervals are narrow and do not cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed.*
- **Confounding factors:** *Absent.*
- **Publication bias:** *Unable to be assessed.*
- **Overall strength of research evidence:** *Moderate.* The two RCTs that assess changing from one antipsychotic to another have good sample sizes and a medium risk of bias. Their findings are consistent with each other and with the results of studies discussed for Statements 4 and 5 on the benefits of antipsychotic medication treatment.

Grading of the Overall Supporting Body of Research Evidence for the Harms of Continuing the Same Antipsychotic Medication

See Appendix C, Statement 4, Grading of the Overall Supporting Body of Research Evidence for Harms of Antipsychotic Medications.

Statement 7: Clozapine in Treatment-resistant Schizophrenia

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

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

* 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.

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-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).

In an additional network meta-analysis of 32 antipsychotic medications, Huhn and colleagues (Huhn et al. 2019) included 402 placebo-controlled and head-to-head randomised controlled trials that included a total of 53,463 adult participants with acute symptoms and a diagnosis of schizophrenia or a related disorder. Studies that focused on individuals with a first-episode of psychosis or treatment resistance were not included as were studies in which individuals had concomitant medical illnesses or a predominance of negative or depressive symptoms. Only clozapine, amisulpride, zotepine, olanzapine, and risperidone exhibited greater efficacy than many other antipsychotic medications for overall symptoms with the greatest benefit noted with clozapine (SMD -0.89, 95% CrI -1.08 to -0.71). Clozapine also was statistically better than placebo and the majority of the other antipsychotic medications in terms of all cause discontinuation (SMD 0.76, 95% CrI 0.59 to 0.92) and its effects on positive symptoms (SMD -0.64, 95% CrI -1.09 to -0.19), negative symptoms (SMD 0.62, 95% CrI -0.84 to -0.39) and depressive symptoms (SMD -0.52, 95% CrI -0.82 to -0.23).

Findings from studies using administrative databases also suggest benefits of treatment with clozapine. For example, a prospective nationwide study conducted over a 7.5-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). Similar benefits of clozapine were found in analysis of prospective registry data from Finland obtained for all persons with schizophrenia who received inpatient care from 1972 to 2014 (Taipale et al. 2018a). Of the 62,250 individuals in the prevalent cohort, 59% were readmitted during follow-up time of up to 20 years (median follow-up duration 14.1 years). Compared with no antipsychotic use, clozapine was associated with the lowest risk of oral antipsychotic medications for psychiatric readmission (HR 0.51, 95% CI 0.49 to 0.53) and for all-cause readmission (HR 0.60, 95% CI 0.58 to 0.61). For the 8,719 individuals with a first episode of schizophrenia, risk of psychiatric readmission and all-cause readmission were also reduced (HR 0.45, 95% CI 0.40 to 0.50 and HR 0.51, 95% CI 0.47 to 0.56, respectively). 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. 2019).

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 ($p<0.001$; NNH=4), seizures ($p<0.05$; NNH=17), tachycardia ($p<0.01$; NNH=7), fever ($p<0.01$; NNH=19), dizziness ($p<0.01$; NNH=11), sedation ($p<0.001$; NNH=7), constipation ($p<0.05$; NNH=12), and nausea or vomiting ($p<0.05$; 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; $p<0.01$).

In the network meta-analysis of Huhn and colleagues (Huhn et al. 2019), individuals treated with clozapine were less likely to require use of an antiparkinson medication (SMD 0.46, 95% CrI 0.19 to 0.88) than with other antipsychotic agents or placebo. However, clozapine was associated with a greater degree of weight gain (SMD 2.37, 95% CrI 1.43 to 3.32), sedation (SMD 3.02, 95% CrI 2.52 to 3.37) and experiencing at least one anticholinergic side effect (SMD 2.21, 95% CrI 1.26 to 3.47) than placebo.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Clozapine in Treatment-resistant Schizophrenia.

- **Magnitude of effect: Moderate.** The magnitude of clozapine's effect varies with the study design and inclusion criteria. Some meta-analyses of RCTs show no difference for clozapine but most studies show significant benefit, at least short-term. Observational studies also show a magnitude of effect that is at least moderate.
- **Risk of bias: Medium.** Studies include RCTs and observational studies, primarily registry studies. Most studies have some limitations based on their descriptions of randomization, blinding procedures, and study dropouts.

- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. Most individuals who receive treatment with clozapine have had at least one trial of another antipsychotic medication and most would meet usual clinical criteria for treatment-resistant schizophrenia, even when this is not well specified in the study description. The doses of medication used are representative of usual clinical practice.
- **Directness:** *Variable.* Studies measure psychotic symptoms, response to treatment, all cause treatment discontinuation, psychiatric hospitalization, all-cause hospitalization, depression, and mortality. Some of these outcomes are directly related to the review questions and some are indirectly related.
- **Consistency:** *Inconsistent.* Although most meta-analyses and observational studies show benefits for clozapine, not all meta-analyses show superiority of clozapine to other antipsychotic medications in individuals with treatment resistant schizophrenia.
- **Precision:** *Variable.* Some confidence intervals are narrow without overlapping the threshold for clinically significant benefits, whereas other confidence intervals are wide or overlapping.
- **Dose-response relationship:** *Present.* Increases in dose and corresponding increases in blood levels of clozapine appear to be related to improved clinical efficacy in non-toxic ranges of dosing.
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Additional monitoring and an increased frequency of clinical contacts with clozapine may enhance the effects of the medication relative to other antipsychotic medications, at least in observational studies.
- **Publication bias:** *Unclear.* Although publication bias for clozapine-specific studies was not tested, publication bias is relatively common in studies of psychopharmacology due to non-publication of negative studies.
- **Overall strength of research evidence:** *Moderate.* The available studies include RCTs of moderate quality and good sample sizes. The effect sizes for clozapine vary among meta-analyses and outcomes. However, most studies, including RCTs and prospective observational studies, show benefits of clozapine as compared to other antipsychotic medications.

Grading of the Overall Supporting Body of Research Evidence for Harms of Clozapine

- **Magnitude of effect:** *Moderate.* The magnitude of effect is moderate overall but varies with the specific side effect. As compared to other antipsychotic medications, clozapine is associated with a greater risk of weight gain, sialorrhea, sedation, metabolic effects, seizures, constipation, anticholinergic side effects, tachycardia, and dizziness but a lower risk of all cause treatment discontinuation, extrapyramidal side effects, or need for anticholinergic medication.
- **Risk of bias:** *Medium.* Studies include RCTs and a large observational study of patient-reported side effects. RCTs are of low to medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts, whereas the observational study has a high risk of bias.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The doses of medication used are representative of usual clinical practice.

- **Directness:** *Variable.* Studies measure observed and reported side effects of clozapine, as well as treatment discontinuation (all cause and due to adverse effects).
- **Consistency:** *Consistent.* Study findings are consistent in the relative magnitude and direction of effects for specific side effects and for treatment discontinuation.
- **Precision:** *Precise.* Confidence intervals are narrow and do not cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed.* However, clinical observations suggest that many side effects do increase in occurrence or severity with the dose of clozapine.
- **Confounding factors:** *Unclear.* Not all studies assess side effects in a systematic fashion and patients may be less likely to report some side effects if they are not directly assessed.
- **Publication bias:** *Not assessed.* Nevertheless, publication bias is relatively common in studies of psychopharmacology due to non-publication of negative studies.
- **Overall strength of research evidence:** *Low to moderate.* Available studies include RCTs and an observational study. Data from several meta-analyses suggest a moderate strength of research evidence for outcomes related to clozapine harms but the AHRQ review found a low strength of research evidence in a network meta-analysis and the observational study also has a high risk of bias.

Other Interventions for Treatment-resistant Schizophrenia

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).

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 20 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 19 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. In contrast, in another randomized trial of 23 patients who received 12 sessions of ECT as compared to sham ECT, no differences were found PANSS score reductions although both groups showed improvement during the study (Melzer-Ribeiro et al. 2017)

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 (G. Wang et al. 2018) 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 $p\leq 0.0001$, 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 seven 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. 2019b) 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 three weeks with five 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 8: Clozapine in Suicide Risk

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

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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 (five for clozapine and three 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 five 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 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 six 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 7.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Clozapine in Individuals With Substantial Risk Factors for Suicide Attempts or Suicide

- **Magnitude of effect:** *Moderate to Strong*. In the InterSePT RCT, moderate effects are present for clozapine as compared to olanzapine in reducing suicide attempts and hospitalizations to prevent suicide. As compared to other antipsychotic medications, larger effects of clozapine on suicide attempts and suicide are found in observational registry studies with longer periods of follow-up and larger sample sizes.
- **Risk of bias:** *Medium*. Studies include an RCT and observational studies. There is low risk of bias in the RCT on most outcomes but a medium to high risk of bias for the observational studies due to their lack of randomization, lack of blinding, and retrospective study design.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. Doses of clozapine used in the RCT are representative of usual clinical practice. In addition, the RCT includes individuals with an increased risk of suicide whereas the observational studies assessed suicide-related outcomes without pre-selecting for high risk individuals. Nevertheless, rates of suicide are increased among individuals with schizophrenia making the observational study findings of relevance to routine clinical practice.
- **Directness:** *Variable*. In the RCT, studies measured suicide attempts and deaths due to suicide, but mortality was infrequent making statistical comparisons invalid. For the observational studies,

suicide attempts and deaths by suicide were also studied. Nevertheless, observational study findings are indirect due to the lack of selection of patients at high risk of suicide.

- **Consistency:** *Consistent.* Reductions in suicide attempts are consistent in the RCT and in observational studies. The reduction in suicide deaths in larger samples with longer follow-up periods is consistent with the reduction in suicide attempts.
- **Precision:** *Precise.* Confidence intervals are narrow and do not cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed.*
- **Confounding factors:** *Present.* In the RCT, effects on suicide deaths may be reduced by the need to intervene with increased monitoring, hospitalization, or study withdrawal if suicidal risk is significant. Additional monitoring and an increased frequency of clinical contacts with clozapine may enhance the effects of the medication relative to other antipsychotic medications, at least in observational studies.
- **Publication bias:** *Unable to be assessed.* The small number of relevant studies makes assessment of publication bias impossible.
- **Overall strength of research evidence:** *Moderate.* In terms of clozapine effects on suicidal behaviors and suicide, available studies include an RCT and several observational studies with large samples and long periods of follow-up. Confidence intervals are relatively narrow, and the findings are consistent.

Grading of the Overall Supporting Body of Research Evidence for Harms of Clozapine in Individuals With Substantial Risk Factors for Suicide Attempts or Suicide

See Appendix C, Statement 7, Grading of the Overall Supporting Body of Research Evidence for Harms of Clozapine.

Statement 9: Clozapine in Aggressive Behavior

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

* 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.

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 7.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Clozapine in Individuals With Substantial Risk Factors for Aggressive Behaviors

- **Magnitude of effect:** *Unclear.* Available studies report statistical superiority but there are no good estimates of the magnitude effect either within or among studies.
- **Risk of bias:** *High.* Most of the available studies, including RCTs and open-label studies, have a significant risk of bias and a lack of reported details about randomization, blinding, and other features of study design.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. Most studies are focused on inpatients, including forensic psychiatry populations, who exhibit physically assaultive behavior. The doses of medication used are within normal to high dose ranges for usual clinical practice.
- **Directness:** *Variable.* Studies measure multiple different outcomes including hostility items on PANSS or BPRS, time in restraint, episodes of restraint, or episodes of assaultive behavior.
- **Consistency:** *Consistent.* Studies generally report reductions in hostility or aggressive behavior.
- **Precision:** *Unknown.* Confidence intervals are not reported in all studies or in the available meta-analysis. Nevertheless, a lack of precision is likely due to the small samples in most studies.
- **Dose-response relationship:** *Not assessed.*
- **Confounding factors:** *Present.* In observational outpatient studies, additional monitoring and an increased frequency of clinical contacts with clozapine may enhance medication effects relative to other antipsychotic medications. The high risk of bias in many of these studies suggests that confounding factors may be present but unrecognized.
- **Publication bias:** *Unable to be assessed.* The relatively small number of studies and the heterogeneity of study designs make it difficult to assess publication bias. However, publication bias seems possible due to the tendency for negative clinical trial results to go unpublished.
- **Overall strength of research evidence:** *Low.* The available studies include RCTs and open-label studies with a high risk of bias. Although the findings are consistent, the applicability to typical clinical practice is limited. Other sources of possible bias were unable to be assessed but are likely to be present.

Grading of the Overall Supporting Body of Research Evidence for Harms of Clozapine in Individuals With Substantial Risk Factors for Aggressive Behaviors

See Appendix C, Statement 7, Grading of the Overall Supporting Body of Research Evidence for Harms of Clozapine

Statement 10: Long-acting Injectable Antipsychotic Medications

APA suggests (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*

Evidence for this guideline statement comes from the AHRQ review (McDonagh et al. 2017) as well as from other randomized controlled trials, registry database studies, cohort studies, mirror image studies and meta-analyses of such trials. The findings from these studies are mixed because RCTs show few differences in outcomes between LAI antipsychotic medications and oral antipsychotic agents whereas observational trials show consistent benefits of LAI formulations. There are a number of possible explanations for these apparent disparities related to the design of the studies and differences in study populations (Correll et al. 2016; Fagiolini et al. 2017). Individuals who are agreeable to participating in a randomized clinical trial are more likely to be adherent to treatment than a broader population of individuals with a particular diagnosis. A greater focus on adherence-related questions and a greater frequency of visits may occur in an RCT as compared to treatment as usual, which may also influence adherence or outcomes. Consequently, the possible advantages of LAIs over oral formulations in promoting or assuring adherence may be less salient in RCTs as compared to observational trials. Although each type of study has advantages and disadvantages, observational trials that use registry databases are also able to examine outcomes among large numbers of individuals over many years of follow-up in contrast to the smaller numbers and shorter follow-up periods of RCTs.

In the AHRQ review (McDonagh et al. 2017), the ability to draw conclusions about the comparative effectiveness of LAI antipsychotic medications is limited by the relatively small number of head-to-head comparison studies among LAI antipsychotic medications or for LAI formulations as compared to oral agents. Few studies assessed differences in symptoms with treatment, but clozapine was noted to be superior to aripiprazole LAI (monthly or every six weeks), olanzapine LAI, paliperidone LAI (monthly and every three months) and risperidone LAI whereas paliperidone LAI every three months was superior to oral lurasidone (low SOE). For the few comparisons where data on response was available, no differences were found (low SOE). Risperidone LAI was significantly better than quetiapine in social function over 24 months but did not differ from quetiapine on measures of quality of life (low SOE). No difference in social function was found between paliperidone palmitate monthly LAI and risperidone bi-weekly LAI (low SOE). In terms of quality of life, oral aripiprazole and aripiprazole monthly LAI did not differ from one another with up to two years of follow-up (low SOE).

In terms of findings on harms, a network meta-analysis of 90 head-to-head RCTs showed that risperidone LAI had a significantly lower risk of withdrawal due to adverse events than 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 (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); or ziprasidone (OR 0.40, 95% CI 0.20 to 0.82). No differences in overall adverse events were found between aripiprazole as compared to aripiprazole monthly LAI or between paliperidone or paliperidone palmitate monthly LAI as compared to risperidone LAI (low SOE). In addition, no differences in extrapyramidal side effects were seen in a 28-

* 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.

week trial of aripiprazole and paliperidone monthly LAI or a network meta-analysis comparing monthly and four to six week LAI of aripiprazole. However, aripiprazole monthly LAI had a greater incidence of extrapyramidal side effects (RR 1.88) and worse akathisia than oral aripiprazole short-term but not at one-year. For mortality, no significant difference was found between paliperidone palmitate monthly LAI versus risperidone LAI (RR 1.26, 95% CI 0.21 to 7.49) based on two RCTs of four to 24 months duration (low SOE).

A number of other meta-analyses of RCTs are also available and provide complementary information to the findings in the AHRQ review. Ostuzzi and colleagues (Ostuzzi et al. 2017) conducted a systematic review and meta-analysis of RCTs that compared the oral and LAI formulations of the same antipsychotic medication and included risperidone (six studies), olanzapine (two studies), aripiprazole (three studies), zuclopenthixol (one study), fluphenazine (seven studies) and haloperidol (two studies). There was a small benefit for LAI aripiprazole (two studies, N=986; RR 0.78, 95% CI 0.64 to 0.95; high SOE) as compared to oral aripiprazole for all-cause discontinuation, a small benefit for oral olanzapine as compared to LAI olanzapine for discontinuation due to inefficacy (two studies, N=1,445; RR 1.52, 95% CI 1.12 to 2.07; low SOE), and a small benefit for LAI risperidone as compared to oral risperidone for hyperprolactinemia (five studies, N=891; RR 0.81, 95% CI 0.68 to 0.98; moderate SOE). The other comparisons showed no differences for these outcomes and there were also no differences noted for non-response rate, relapse rate, dropouts for adverse events, extrapyramidal symptoms, or weight gain.

Kishimoto and colleagues (Kishimoto et al. 2014) examined the relative efficacy of LAI antipsychotic medications as compared to oral antipsychotic medications in relapse prevention and found that LAIs were similar to oral agents in outpatient studies lasting \geq one year (12 studies; RR 0.93, 95% CI 0.71 to 1.07; $p=0.31$) and at the longest study time point across all settings (21 studies, N=4,950; RR 0.93, 95% CI: 0.80-1.08; $p=0.35$). When analyzed by drug, LAI fluphenazine showed greater benefit in preventing relapse (RR 0.79, 95% CI 0.65 to 0.96; $P=0.02$) than oral antipsychotic agents; however, the authors note that this may be mediated by a cohort effect rather than a drug specific effect as all of the fluphenazine studies were predated 1992. For drug inefficacy, calculated as the sum of relapses plus discontinuations due to inefficacy, LAI fluphenazine was again superior to oral antipsychotic agents (eight studies, N=826; RR 0.78, 95% CI 0.66 to 0.91; $p=0.002$) whereas olanzapine LAI was inferior to oral antipsychotic agents (N=1,445; RR 1.52, 95% CI 1.12 to 2.07; $p=0.007$). LAI fluphenazine was also superior to oral antipsychotic agents in preventing hospitalization (four studies, N=197; RR 0.82, 95% CI 0.67 to 0.99, $P=0.04$) in contrast to pooled data for LAIs as compared to oral antipsychotic agents in preventing hospitalization (10 studies, N=2,296; RR 0.88, 95% CI 0.75 to 1.03; $P=0.09$). No differences in all-cause discontinuation were noted in pooled analyses or for individual LAIs (fluphenazine, haloperidol, zuclopenthixol, risperidone, olanzapine).

A separate meta-analysis (Kishi et al. 2016b) examined the efficacy of LAI paliperidone or LAI risperidone as compared to oral antipsychotic agents in patients with a recent-onset psychotic disorder. Although there was significant heterogeneity in the study findings, LAIs and oral agents were comparable overall in relapse prevention (three studies; N=875). The LAIs did have fewer study discontinuations due to inefficacy (RR 0.34, NNT=-50) or nonadherence (RR 0.30, NNT=-33), but LAIs also had a higher incidence of tremor (RR 2.38) or at least one adverse effect (RR 1.13). In terms of mortality with LAIs as compared

to oral antipsychotic agents, another meta-analysis of 52 RCTs found no difference between LAIs and placebo or oral antipsychotics in all-cause death or death due to suicide (total N=17,416; LAI antipsychotics=11,360, oral antipsychotics=3,910, and placebo=2,146; LAI antipsychotics vs placebo=28.9, LAI antipsychotics vs oral antipsychotics=64.5; Kishi et al. 2016a)

An additional RCT is the Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy (PROACTIVE) study of Buckley and colleagues (Buckley et al. 2015). This multi-site trial was conducted at eight academic centers in the U.S. and randomly assigned patients with schizophrenia or schizoaffective disorder to LAI risperidone or the physician's choice of an oral SGA for up to 30 months. Subjects were outpatients who were neither resistant to treatment nor in a first episode of psychosis. Approximately half of the subjects (161 of 305) discontinued treatment before the end of the trial. There was no significant difference noted in the proportion with a relapse (42% for LAI risperidone vs. 32% for oral SGA; $p=0.08$), time to first relapse ($p=0.13$) or time to first hospitalization ($p=0.30$). In addition, no significant differences between LAI risperidone and oral SGAs were noted for the bulk of symptom ratings (anxiety-depression, negative symptoms, excitement, affective flattening, avolition, asociality-anhedonia, CGI severity and improvement, two Scale of Functioning measures). However, changes in symptom scores did differ between the treatment arms with lower SANS alogia scores with oral SGAs and greater improvement in psychotic symptoms and BRPS total scores with LAI risperidone. In patients followed after an initial relapse, 32 (11%) had two relapses and 13 (4%) had three relapses with no significant differences in the rate or time to successive relapse between those treated with LAI risperidone as compared to oral SGAs (Buckley et al. 2016).

In contrast to the findings from RCTs, observational studies often find benefits of LAI antipsychotic formulations as compared or oral antipsychotic formulations. Tiihonen and colleagues (Tiihonen et al. 2017) used a prospective national database in Sweden and used individuals as their own controls to examine the risk of psychiatric rehospitalization or treatment failure defined as psychiatric rehospitalization, admissions due to a suicide attempt, discontinuation or switch to other antipsychotic medication, or death. Of the 29,823 patients, 43.7% were rehospitalized and 71.7% met criteria for treatment failure. The LAI formulations of antipsychotic medications were associated with a 20% to 30% lower risk of rehospitalization as compared to oral formulations of antipsychotic (HR 0.78, 95% CI 0.72 to 0.84 for the total cohort; HR 0.68, 95% CI 0.53 to 0.86 for the incident cohort). For specific LAI antipsychotic medications as compared with no use of antipsychotic medication, rehospitalization risk was lowest with once-monthly LAI paliperidone (HR 0.51, 95% CI 0.41 to 0.64), LAI zuclopenthixol (HR 0.53, 95% CI 0.48 to 0.57), LAI perphenazine (HR 0.58, 95% CI 0.52 to 0.65), and LAI olanzapine (HR 0.58, 95% CI 0.44 to 0.77). Of the oral medications, rehospitalization rates were lowest with clozapine (HR 0.53, 95% CI 0.48 to 0.58). Rates of treatment failure were also lowest with clozapine (HR 0.58, 95% CI 0.53 to 0.63) and with LAI antipsychotic formulations as compared to other oral formulations (HR values for LAI formulations are LAI perphenazine 0.65, LAI haloperidol 0.67, LAI zuclopenthixol 0.69, LAI paliperidone 0.72, LAI flupentixol 0.75, LAI olanzapine 0.77 and LAI risperidone 0.80).

Tiihonen and colleagues (Tiihonen et al. 2011) also compared LAI antipsychotics to their equivalent oral formulation in a nationwide cohort of 2,588 consecutive patients in Finland who had an initial admission with a diagnosis of schizophrenia. Of those individuals, only 58.2% used an antipsychotic medication

after discharge and 45.7% of the cohort remained on an antipsychotic for at least 30 days. For rehospitalization as well as for all-cause discontinuation, LAI antipsychotic had a lower adjusted hazard ratio (aHR) than the equivalent oral formulation (aHR 0.36, 95% CI 0.17 to 0.75; $p=0.007$ and aHR 0.41, 95% CI 0.27 to 0.61; $p<0.0001$, respectively). For each LAI antipsychotic as compared to its oral equivalent, rehospitalization was lower with LAI haloperidol (aHR 0.12, 95% CI 0.01 to 1.13; $p=0.06$), but not LAI perphenazine (aHR 0.53, 95% CI 0.22 to 1.28; $p=0.16$) or LAI risperidone (aHR 0.57, 95% CI 0.30 to 1.08; $p=0.09$). Use of an LAI antipsychotic was also associated with lower rates of all cause discontinuation for LAI haloperidol, LAI, and LAI risperidone as compared to their oral equivalents (aHR 0.27, 95% CI 0.08 to 0.88; $p=0.03$; aHR 0.32, 95% CI 0.19 to 0.53; $p<0.0001$; and aHR 0.44, 95% CI 0.31 to 0.62; $p<0.0001$, respectively). LAI zuclopenthixol showed no difference from its equivalent oral formulation in either rehospitalization or all-cause discontinuation.

Taipale and colleagues (Taipale et al. 2018a) used the same nationwide Finnish health care registry to assess the long-term effectiveness of antipsychotic medications on the risk of psychiatry re-hospitalization over follow-up periods of up to 20 years (median of 14.1 years). The sample included a prevalence cohort of 62,250 individuals as well as 8,719 individuals who were followed prospectively after a first episode of psychosis. The risk of psychiatric rehospitalization was lower with LAI antipsychotic medications than with oral antipsychotic formulations (LAI FGAs HR 0.46, 95% CI 0.40 to 0.54; LAI SGAs HR 0.45, 95% CI 0.39 to 0.52; oral FGAs HR 0.67, 95% CI 0.60 to 0.74; oral SGAs 0.57, 95% CI 0.53 to 0.61) in first-episode patients as was the risk of all-cause hospitalization (LAI FGAs HR 0.58, 95% CI 0.51 to 0.66; LAI SGAs HR 0.56, 95% CI 0.50 to 0.63; oral FGAs HR 0.80, 95% CI 0.74 to 0.87; oral SGAs HR 0.69, 95% CI 0.66 to 0.73), with similar patterns noted in the prevalence cohort.

A nationwide registry was also used by Taipale and colleagues (Taipale et al. 2018b) to examine all-cause mortality and its relationship to medication treatment among patients with schizophrenia in Sweden. Information on 29,823 individuals was available between 2006 and 2013 of which 4603 patients were in the incident cohort. For LAI SGAs, the cumulative mortality rate was about one-third lower than the mortality rate for equivalent oral antipsychotics in pairwise analyses (aHRs 0.67, 95%CI 0.56 to 0.80). Those taking an LAI formulation of an SGA had the lowest cumulative mortality (7.5%) with median follow-up of 6.9 years. Corresponding rates of cumulative mortality were 8.5% for oral SGAs, 12.2% for oral FGAs, 12.3% for LAI FGAs, and 15.2% in those who were not taking an antipsychotic medication. As compared to LAI SGAs, corresponding aHRs were 1.52 (1.13 to 2.05) for oral SGAs, 1.37 (95%CI 1.01 to 1.86) for LAI FGAs, 1.83 (1.33-2.50) for oral FGAs, and 3.39 (2.53-4.56) in those who were not taking an antipsychotic medication.

MacEwan and colleagues (MacEwan et al. 2016b) used a multi-state database of U.S. Medicaid patients to examine the probability of rehospitalization after an index admission with LAI antipsychotic treatment as compared to oral antipsychotic treatment. For 1,450 patients with a diagnosis of schizophrenia, multivariate logistic regression with propensity score matching, use of an LAI antipsychotic medication was associated with a lower probability of readmission at 60 days post-discharge (adjusted OR 0.60, 95% CI 0.41 to 0.90) but not at 30 days post-discharge.

Kishimoto and colleagues (Kishimoto et al. 2013; Kishimoto et al. 2018) conducted meta-analyses of cohort studies and "mirror image" studies to compare the effectiveness of LAIs to oral antipsychotic agents in terms of hospitalization and treatment discontinuation. Based upon 42 prospective and retrospective cohort studies (total N=101,624; mean follow-up=18.6 ± 10.0 mo), LAIs were found to be superior to oral antipsychotics in terms of all-cause discontinuations (10 studies; N= 37,293; risk ratio 0.78, 95% CI 0.67 to 0.91; p=0.001) and hospitalization rates (15 studies, 68,009 person-years; rate ratio 0.85, 95% CI 0.78 to 0.93; p<0.001), but not hospitalization risk or days of hospitalization (Kishimoto et al. 2018). However, the patients treated with an LAI antipsychotic medication had longer illness durations than those treated with oral formulations of antipsychotic medication, which may have influenced the findings. In 25 "mirror image" studies that followed patients for at least six months before and after a transition between medication formulations, LAI antipsychotic medications were superior to oral antipsychotic medications in preventing hospitalization (16 studies, N=4,066; risk ratio 0.43, 95% CI 0.35 to 0.53; P<0.001) and in decreasing the number of hospitalizations (15 studies, 6,342 person-years; rate ratio 0.38, 95% CI 0.28 to 0.51; P<0.001) (Kishimoto et al. 2013).

Grading of the Overall Supporting Body of Research Evidence for the Efficacy of LAI Antipsychotic Medications

- **Magnitude of effect:** *Variable*. In RCTs, there are few differences in outcomes between LAI and oral formulations of antipsychotic medications. However, significant benefits with a moderate magnitude of effect are noted in observational studies including prospective registry database studies and "mirror image" studies.
- **Risk of bias:** *Medium*. Studies include RCTs that have some limitations in study design or reporting of features such as randomization or blinding. Observational studies based on prospective registry data are well-designed but have at least a medium risk of bias due to a lack of randomization or blinding.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with schizoaffective disorder. The doses of medication used are not always stated but appear to be representative of usual clinical practice. The observational studies include data from a nationwide registry and have broad generalizability in contrast to RCTs with more restrictive inclusion and exclusion criteria. However, the applicability of registry data from Nordic countries may be reduced by differences in the health care delivery system as compared to the U.S.
- **Directness:** *Variable*. Most studies measure direct outcomes including differences in symptoms, quality of life, functioning, relapse prevention, and rehospitalization. However, some studies assess indirect outcomes including all-cause treatment discontinuation.
- **Consistency:** *Inconsistent*. RCTs generally show little or no benefit of LAI as compared to oral formulations of antipsychotic medications whereas observational studies showed moderate benefits. However, findings were consistent for different types of observational studies including prospective registry database studies and mirror-image analyses.
- **Precision:** *Imprecise*. For RCTs, confidence intervals cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed*.

- **Confounding factors:** *Unclear.* Confounding factors may be present for the observational studies due to the lack of randomization. However, individuals with poor adherence or more severe symptoms may more likely to receive an LAI, which would favor oral medications on outcomes such as relapse or rehospitalization.
- **Publication bias:** *Not suspected.* Publication bias was not detected in the meta-analyses that specifically examined this question.
- **Overall strength of research evidence:** *Moderate.* Available evidence includes data from several types of observational studies, each of which shows consistent benefits for LAI as compared to oral formulations of antipsychotic medication. The potential benefit of LAI formulations in assuring adherence may not be observable in RCTs in which patients are already selected for high adherence. Although trials are of varying quality, most have good sample sizes. When beneficial effects are noted, most confidence intervals are narrow. There is some variation from drug to drug, but registry data show better outcomes with LAI formulations as a group as compared to oral formulations of antipsychotic medication as a group.

Grading of the Overall Supporting Body of Research Evidence for the Harms of LAI Antipsychotic Medications

- **Magnitude of effect:** *Variable.* In general, there appear to be few differences between harms of LAI antipsychotic medications and oral formulations of antipsychotic medications, particularly when LAI and oral formulations of the same drug are compared. When differences are noted in rates of specific side effects, the magnitude of those effects is weak.
- **Risk of bias:** *Medium.* In RCTs, some limitations in study design are present. In other studies, harms of treatment were not systematically assessed.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. The doses of medication used are not always stated but appear to be representative of usual clinical practice. The observational studies include data from a nationwide registry and have broad generalizability in contrast to RCTs with more restrictive inclusion and exclusion criteria. However, the applicability of registry data from Nordic countries may be reduced by differences in the health care delivery system as compared to the U.S.
- **Directness:** *Variable.* When assessments of adverse effects are conducted, studies measure specific side effects. However, other studies measure study withdrawals due to adverse effects.
- **Consistency:** *Inconsistent.* Some comparisons show differences between LAI and oral formulations on specific side effects, but these are not consistent among medications or meta-analyses.
- **Precision:** *Imprecise.* Confidence intervals cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed.* Data from studies of oral medications suggest that increases in dose are likely to be associated with increases in medication side effects.
- **Confounding factors:** *Unclear.* Adverse effects are not always assessed in a systematic fashion and reporting biases may be present.

- **Publication bias:** *Not suspected.* Publication bias was not detected in the meta-analyses that specifically examined this question.
- **Overall strength of research evidence:** *Low.* Available studies include RCTs that assess side effects of LAI and oral formulations of antipsychotic medications. Meta-analyses and network meta-analyses are also available that include head-to-head comparison trials. In terms of ascertainment and reporting of information on side effects, studies have at least a medium risk of bias and there is significant inconsistency in the findings among the available studies, making it difficult to draw conclusions with any degree of confidence.

Statement 11: Anticholinergic Medications for Acute Dystonia

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.

Grading of the Overall Supporting Body of Research Evidence for Anticholinergic Medications for Acute Dystonia

Based on the limitations of the evidence for anticholinergic medications for acute dystonia, no grading of the body of research evidence is possible.

Statement 12: Treatments for Parkinsonism

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.

Grading of the Overall Supporting Body of Research Evidence for Treatments for Parkinsonism

Based on the limitations of the evidence for treatments for parkinsonism, no grading of the body of research evidence is possible.

Statement 13: Treatments for Akathisia

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.

Grading of the Overall Supporting Body of Research Evidence for Treatments for Akathisia

Based on the limitations of the evidence for treatments for akathisia, no grading of the body of research evidence is possible.

Statement 14: VMAT2 Medications for Tardive Dyskinesia

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).

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 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 four 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 KINECT3 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, 1971), and another double-blind crossover trial of 24 subjects (Kazamatsuri et al. 1972). Although 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., deutetrabenazine, tetrabenazine, valbenazine), the guideline writing group also reviewed evidence for other possible treatments for tardive dyskinesia. Amantadine has 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. Other studies of treatments for tardive dyskinesia have been discussed in systematic reviews as summarized in Table C-2. Based on these findings, there is insufficient evidence to support a guideline statement on use of these treatments in individuals with tardive dyskinesia.

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

Intervention	Citation	Comments
Anticholinergic agents	Bergman and Soares-Weiser 2018	Two trials (total N=30) of very low-quality evidence
Benzodiazepines	Bergman et al. 2018a	Four trials (total N=75) of very low-quality evidence showed no clinically significant difference relative to placebo
Calcium channel blockers	Soares-Weiser and Rathbone 2011	No studies met inclusion criteria
Cessation or reduction of antipsychotic	Bergman et al. 2018b	Two trials (total N=17) with very low-quality evidence
Change to clozapine	Mentzel et al. 2018	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).
Cholinergic medication	Tammenmaa-Aho et al. 2018	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.
Gamma-aminobutyric acid agonists	Alabed et al. 2011	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.
Ginkgo biloba extract	Soares-Weiser et al. 2018b	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.
Non-antipsychotic catecholaminergic drugs	El-Sayeh et al. 2018	10 trials (N=261) with very low-quality evidence and one to two trials per therapeutic comparison
Vitamin B6 (Pyridoxal 5 phosphate)	Adelufosi et al. 2015	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.
Vitamin E	Soares-Weiser et al. 2018a	13 trials (total N=478) of low quality showed possible blunting of additional deterioration but no clear difference when compared with placebo in terms of clinically important improvement
Miscellaneous agents, including branched chain amino acids, buspirone, dihydrogenated ergot alkaloids, estrogen, gamma-linolenic acid,	Soares-Weiser et al. 2018b	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

insulin, isocarboxazid, lithium, melatonin, pemoline, promethazine, ritanserin, and selegiline		
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Abbreviations: CI=confidence interval; RR=relative risk

Grading of the Overall Supporting Body of Research Evidence for Efficacy of VMAT2 Inhibitors

- **Magnitude of effect:** *Moderate*. Effects are at least moderate in terms of the proportion of individuals who are much improved or very much improved with valbenazine or deutetrabenazine as compared to placebo. Statistically significant differences are also found for rates of response and for decreases in total AIMS scores. Less data is available for tetrabenazine and its magnitude of effect is unclear
- **Risk of bias:** *Low to medium*. Studies are RCTs with a low to medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with moderate to severe tardive dyskinesia, although some studies include individuals with diagnoses other than schizophrenia. The doses of medication used are representative of usual clinical practice.
- **Directness:** *Direct*. Studies measure changes in signs of tardive dyskinesia on the AIMS and proportions of individuals who showed at least 50% response or who were much improved or very much improved on a global measure of benefit.
- **Consistency:** *Consistent*. Studies are consistent in showing benefits of valbenazine and deutetrabenazine. Studies of tetrabenazine are more limited in number, sample size, and design but also show benefit in individuals with tardive dyskinesia.
- **Precision:** *Imprecise*. Confidence intervals are wide but do not cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Present*. Valbenazine and deutetrabenazine show an increase in clinical benefit with an increase in dose.
- **Confounding factors:** *Unclear*. No specific confounding factors are noted for valbenazine or deutetrabenazine, but confounding factors may be present for tetrabenazine due to weaknesses in study methodologies.
- **Publication bias:** *Unable to be assessed*. The small number of available studies precludes assessment of publication bias.
- **Overall strength of research evidence:** *Moderate*. The available studies of valbenazine and deutetrabenazine are of good quality with good sample sizes. However, not all confidence intervals are narrow. In addition, the duration of the randomized phase of the trials was relatively short and as little as four to six weeks in some studies. The long-term follow-up data is based only on open-label extension phases of these RCTs. Data on tetrabenazine has a higher risk of bias, smaller samples sizes, and inadequate blinding, yielding a low strength of research evidence.

Grading of the Overall Supporting Body of Research Evidence for Harms of VMAT2 Inhibitors

- **Magnitude of effect:** *Minimal to weak.* For deutetrabenazine and valbenazine, there are no significant differences from placebo in rates of adverse effects. For tetrabenazine, some adverse effects are more frequent than with placebo, but the magnitude of the difference is still relatively small.
- **Risk of bias:** *Medium to high.* Studies of valbenazine and deutetrabenazine determine adverse events in a systematic fashion but the duration of the randomized phase of the clinical trials is relatively short and the open-label extension phases have a greater risk of bias. Studies of tetrabenazine have a greater number of limitations in study design with a high risk of bias overall.
- **Applicability:** The included trials all involve individuals with moderate to severe tardive dyskinesia, although some studies include individuals with diagnoses other than schizophrenia. The doses of medication used are representative of usual clinical practice.
- **Directness:** *Direct.* Studies measure occurrence of specific side effects.
- **Consistency:** *Variable.* Studies of deutetrabenazine and valbenazine are consistent in showing negligible side effects as compared to placebo. Studies of tetrabenazine generally show greater rates of some side effects than placebo.
- **Precision:** *Imprecise.* Confidence intervals cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not assessed.* Although effects of dose on side effects were not evaluated, dose-response relationships are noted for efficacy of valbenazine and deutetrabenazine.
- **Confounding factors:** *Unclear.* No specific confounding factors are noted for valbenazine or deutetrabenazine, but confounding factors may be present for tetrabenazine due to weaknesses in the study methodologies.
- **Publication bias:** *Unable to be assessed.* The small number of available studies precludes assessments of publication bias.
- **Overall strength of research evidence:** *Low.* Available studies of valbenazine and deutetrabenazine include RCTs of short duration, as well as longer term open-label follow-up phases. Findings for these medications are consistent in showing no apparent difference in side effects relative to placebo. For tetrabenazine, studies have significant limitations and a high risk of bias but show more frequent side effects than placebo. Overall, studies are generally applicable to individuals with moderate to severe tardive dyskinesia, including individuals with a diagnosis of schizophrenia.

Psychosocial Interventions

Statement 15: Coordinated Specialty Care Programs

APA recommends (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care 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

* 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.

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.

Many studies of coordinated specialty care programs were not included in the AHRQ review although there is a long history of using such programs worldwide for early identification and treatment of attenuated psychosis syndrome, related syndromes of high psychosis risk or first-episode psychosis (Addington et al. 2017b; Cotton et al. 2016; Malla and McGorry 2019); however, these programs were not within the scope of this guideline recommendation because they include individuals who do not have a psychiatric diagnosis or who have diagnoses other than schizophrenia at later follow-up times (Fusar-Poli et al. 2016; Iorfino et al. 2019). Only one of the studies in a meta-analysis of early intervention programs (Marshall and Rathbone 2011) was included in the AHRQ analysis; all other studies were excluded due to factors such as small sample size, enrollment of inpatients, lack of applicability to the United States population, and/or use of a one-off intervention.

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 coordinated specialty care program 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. Coordinated specialty care 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 five years after treatment discontinuation. In addition, as compared to usual care, there were no significant effects of coordinated specialty care 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 7.560) 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 coordinated specialty care 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 two years after enrollment as compared to usual care but rates of all-cause mortality were lower in the coordinated specialty care 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 coordinated specialty care 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).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Coordinated Specialty Care Programs

- **Magnitude of effect:** *Moderate*. Significant benefits of coordinated specialty care programs are present for reducing relapse and retention in treatment with less prominent effects on quality of life and functioning.
- **Risk of bias:** *Medium*. Studies are RCTs with a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia as well as individuals with a first episode of psychosis in the context of other diagnoses. Coordinated specialty care programs in usual practice have been developed as a result of research on Coordinated specialty care programs and would be expected to be comparable.
- **Directness:** *Direct*. Studies measure core illness symptoms, functioning, quality of life, relapse, and treatment retention.
- **Consistency:** *Consistent*. Findings are generally consistent among the available RCTs.
- **Precision:** *Variable*. Confidence intervals are generally narrow and do not cross the threshold for clinically significant benefit of the intervention for the majority of outcomes. For some outcomes, however, imprecision was noted due to wide confidence intervals.
- **Dose-response relationship:** *Not assessed*. Studies do not examine effects of varying treatment duration or visit frequency.
- **Confounding factors:** *Present*. Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Unable to be assessed*. A small number of studies meet inclusion criteria for the AHRQ review, which precludes assessment of publication bias.
- **Overall strength of research evidence:** *Moderate*. The strength of research evidence is moderate for most outcomes, although a high strength of evidence is noted for rates of treatment retention with a low strength of research evidence for housing status and core illness symptoms as measured by the PANSS. Neither of the latter outcomes showed an effect of coordinated specialty care programs. Trials vary in sample size, but several had large samples and findings were generally consistent among the available RCTs.

Grading of the Overall Supporting Body of Research Evidence for Harms of Coordinated Specialty Care Programs

Harms of coordinated specialty care programs were not systematically studied and no grading of the evidence for harms is possible.

Statement 16: Cognitive-behavioral Therapy

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

* 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.

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; $I^2=68%$; 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 eight weeks to five 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 (six trials; MD 5.35, 95% CI 1.05 to 9.65; $I^2=77%$). 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 CBTp 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).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Cognitive-behavioral Therapy for Psychosis.

- **Magnitude of effect:** *Moderate*. With outcomes for which an effect is observed (such as core illness symptoms and short-term functioning improvements), there is a moderate magnitude of benefit. For other outcomes, no benefit is seen, or evidence is inconclusive.
- **Risk of bias:** *Medium*. Studies in meta-analyses and other RCTs have a moderate degree of study limitations based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. Some studies also include individuals with other diagnoses such as schizoaffective disorder. When delivered in clinical practice, CBTp may be conducted with a lesser degree of fidelity than when delivered in research contexts.

- **Directness:** *Direct.* Studies measure core illness symptoms, negative symptoms, and social, occupational, and global function.
- **Consistency:** *Variable.* For outcomes with an observed effect, study findings are consistent. For outcomes with no observed effect, study findings are less consistent.
- **Precision:** *Precise.* Confidence intervals are narrow and do not cross the threshold for clinically significant benefit of the intervention for outcomes with an observed effect. For outcomes with no observed effect, findings are imprecise for most outcomes.
- **Dose-response relationship:** *Not assessed.* The impact of differences in the numbers or frequency of treatment sessions is unclear.
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Unclear.* At least one meta-analysis of CBTp suggests that publication bias may be present but analysis for possible publication bias was not available based on all of the included studies.
- **Overall strength of research evidence:** *Moderate.* For outcomes that show an effect of CBTp, there is a moderate strength of research evidence. For other outcomes that did not show an effect, the strength of research evidence is low or insufficient.

Grading of the Overall Supporting Body of Research Evidence for Harms of Cognitive-behavioral Therapy for Psychosis.

Harms of cognitive behavior therapy for psychosis were rarely reported in studies of CBTp and not systematically studied. Information was only available from a single RCT and the AHRQ report notes that the evidence is insufficient to draw any conclusions (McDonagh et al. 2017). Thus, no grading of the evidence for harms is possible.

Statement 17: Psychoeducation

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 five 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 six trials, psychoeducation had a greater effect than usual care on relapse rates (with or without readmission) at nine to 18 months of follow-up (RR 0.80, 95% CI 0.70 to 0.92; moderate SOE). Psychoeducation was also

* 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.

superior to usual care in terms of global functional outcomes at one 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).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Psychoeducation

- **Magnitude of effect:** *Weak*. A modest benefit is seen for psychoeducation in terms of relapse rates and global functional outcomes. Effects on other outcomes are less robust or inconclusive.
- **Risk of bias:** *Medium*. Studies are RCTs, including RCTs as part of a meta-analysis, and have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. There is considerable variability in the content and format of interventions; however, variability is also present in the delivery of psychoeducation in usual clinical practice.
- **Directness:** *Direct*. Studies measure relapse rates, symptoms, functioning, and quality of life.
- **Consistency:** *Consistent*. When outcome data are available from multiple studies, findings are consistent.
- **Precision:** *Variable*. The confidence interval is narrow for relapse at 9 to 18 months, but other outcomes have wide confidence intervals.
- **Dose-response relationship:** *Not assessed*.
- **Confounding factors:** *Present*. Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Unclear*. The most recent meta-analysis of psychoeducation in schizophrenia did not assess whether publication bias was present.
- **Overall strength of research evidence:** *Moderate*. Available RCTs on effects of psychoeducation have reasonable sample sizes and precise, consistent findings on relapse. For functioning, the overall strength of research evidence is low.

Grading of the Overall Supporting Body of Research Evidence for Harms of Psychoeducation

Harms of psychoeducation were only reported in a few studies but appeared comparable to usual care; no grading of the evidence for harms is possible due to the small amount of available evidence.

Statement 18: Supported Employment Services

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 two 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 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 (four 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). In terms of outcomes unrelated to work, findings are less consistent but suggest potential advantages to supported employment in reducing symptoms and hospitalization risk (Burns et al. 2007; Hoffmann et al. 2014; Luciano et al. 2014).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Supported Employment Services

- **Magnitude of effect:** *Moderate*. Moderate effects are present for the proportion of individuals attaining competitive employment or any form of paid employment as compared to usual care or vocational training comparisons.
- **Risk of bias:** *Medium*. Studies are RCTs (including meta-analyses of RCTs) and have a medium risk of bias based on descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. Supported employment interventions, particularly those using the individual placement and support model, appear to be representative of usual clinical practice.

- **Directness:** *Direct.* Studies measure the duration of competitive employment and the proportion of individuals attaining paid or competitive employment, as well as less direct outcomes such as wages earned.
- **Consistency:** *Consistent.* When outcome data are available from more than one study, findings are consistent. In addition, several meta-analyses using somewhat different inclusion and exclusion criteria reached similar findings.
- **Precision:** *Precise.* Narrow confidence intervals are present for the proportion of individuals in competitive employment or working at least 20 hours per week, as well as for mean weeks worked and mean wages earned.
- **Dose-response relationship:** *Not assessed.*
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Suspected.* There appears to be a lack of reporting of smaller trials with negative results based on network meta-analysis and associated funnel plots to identify publication bias (Suijkerbuijk et al. 2017).
- **Overall strength of research evidence:** *Moderate.* There is a moderate overall strength of research evidence for the proportion of individuals attaining competitive employment, any form of paid employment, mean weeks worked, or monthly wages earned as compared to usual care or vocational training comparisons. Trials are of varying quality, but many have a good sample size; large numbers of study subjects are included in meta-analyses.

Grading of the Overall Supporting Body of Research Evidence for Harms of Supported Employment Services

Harms of supported employment services were not systematically studied and no grading of the evidence for harms is possible.

Statement 19: Assertive Community Treatment

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).*

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

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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; $I^2=73\%$), 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; $I^2=34\%$), homeless (four trials; OR 0.20, 95% CI 0.09 to 0.47; $I^2=52\%$), or living non-independently (four trials; OR 0.52, 95% CI 0.35 to 0.79; $I^2=0\%$) 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, 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 three 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; $I^2=0\%$), imprisonment (four trials, total N=471; OR 1.19, 95% CI 0.70 to 2.01; $I^2=27\%$), or police contacts (two trials, total N=149; OR 0.76, 95% CI 0.32 to 1.79; $I^2=84\%$) 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.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Assertive Community Treatment

- **Magnitude of effect:** *Moderate*. On several important outcomes, there is at least a moderate effect. These outcomes include treatment discontinuation and likelihood of hospitalization, unemployment, or homelessness. On other outcomes, however, there is no difference between ACT and treatment as usual.
- **Risk of bias:** *Medium*. Evidence comes from an RCT and a meta-analysis of RCTs, but individual studies have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. The delivery of ACT in the trials is likely to be representative of usual clinical practice although program fidelity may be diminished in usual practice.

- **Directness:** *Direct.* Studies measured core illness symptoms, functioning, quality of life, employment, housing status, and interactions with the criminal justice system.
- **Consistency:** *Variable.* Findings of benefits for having housing or employment are consistent, whereas other outcomes show inconsistencies among individual studies within the meta-analysis.
- **Precision:** *Imprecise.* Confidence intervals for most outcomes are wide and many cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** *Not applicable.*
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Not assessed.*
- **Overall strength of research evidence:** *Moderate.* A significant number of RCTs of ACT are available and, compared with usual care, show that ACT is associated with a lower likelihood of being unemployed and a lower likelihood of not living independently or being homeless. Many trials are moderate in quality although there is some variability.

Grading of the Overall Supporting Body of Research Evidence for Harms of Assertive Community Treatment

Harms of assertive community treatment were not systematically studied and no grading of the evidence for harms is possible.

Statement 20: Family Interventions

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, 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.

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 0-6 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 25-36 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).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Family Interventions

- **Magnitude of effect:** *Moderate*. For outcomes that show an effect of family interventions, such as effects on relapse rate and illness symptoms, the magnitude of the effect is generally moderate.
- **Risk of bias:** *Medium*. Evidence comes from RCTs, including RCTs in a fair quality systematic review. These studies have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. Studies from China are excluded from the analysis due to concerns about their applicability to North American populations. There is considerable variability in the content and methods of the family interventions that are studied; however, there is also considerable variability in interventions that are delivered in clinical practice.
- **Directness:** *Direct*. Studies measure relapse, core illness symptoms, and outcomes related to functioning.
- **Consistency:** *Consistent*. For outcomes with data from more than one study, findings among the studies are consistent.
- **Precision:** *Imprecise*. Confidence intervals for all outcomes are wide or cross the threshold for clinically significant benefit of the intervention.

- **Dose-response relationship:** *Present.* The strongest evidence for effects of family interventions on relapse occurs in studies that include at least 10 treatment sessions over 7-12 months.
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Not assessed.* The most recent meta-analysis of family interventions did not assess whether publication bias was present.
- **Overall strength of research evidence:** *Moderate.* For relapse at 7-12 months, there is a moderate strength of research evidence, but for most other outcomes, the strength of research evidence is low. The strength of research evidence is influenced by a lack of precision, as well as by the small sample sizes for some of the outcomes.

Grading of the Overall Supporting Body of Research Evidence for Harms of Family Interventions
Harms of family interventions were not systematically studied and no grading of the evidence for harms is possible.

Statement 21: Self-management Skills and Recovery-focused Interventions

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 2010a). 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

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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 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.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Self-management Skills and Recovery-focused Interventions

- **Magnitude of effect:** *Weak*. Modest changes were noted in core illness symptom severity, likelihood of relapse, measures of person-oriented recovery, empowerment, and hope.
- **Risk of bias:** *Medium*. Studies are RCTs, including RCTs as part of a meta-analysis, have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. There is considerable variability in the content and format of delivered interventions; however, there is also wide variation in illness self-management and recovery-focused interventions in clinical practice.
- **Directness:** *Direct*. Studies measure functioning, symptoms, and relapse.
- **Consistency:** *Variable*. Consistent for symptoms and relapse but inconsistent for functioning.
- **Precision:** *Variable*. Precise for symptoms as measured by the BPRS but imprecise for other outcomes due to wide confidence intervals.
- **Dose-response relationship:** *Present*. Effects of illness self-management were less prominent if fewer self-management sessions were completed.
- **Confounding factors:** *Present*. Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Not assessed*.
- **Overall strength of research evidence:** *Low*. Studies are RCTs, including a meta-analysis of RCTs, and have a medium risk of bias. The strength of research evidence is moderate for effects on symptoms; it is low or insufficient for other outcomes. Although a dose-response effect seems to be present increasing confidence in the findings, this is offset by the lack of precision for most outcomes.

Grading of the Overall Supporting Body of Research Evidence for Harms of Self-management Skills and Recovery-focused Interventions

Harms of self-management skills and recovery-focused interventions were not systematically studied and no grading of the evidence for harms is possible.

Statement 22: Cognitive Remediation

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 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).

Although the AHRQ review did not specifically assess cognitive outcomes with cognitive remediation, this has been a major focus of study and the primary target of cognitive remediation as an intervention. Results from meta-analyses (Revell et al. 2015; Wykes et al. 2011) and more recent randomized trials (d'Amato et al. 2011; Donohoe et al. 2018; Gomar et al. 2015; Keefe et al. 2012; McGurk et al. 2016;

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Mueller et al. 2015; Reeder et al. 2017) have been mixed, with significant heterogeneity in the degree of cognitive improvement (if any), the domains of cognitive improvement, and the persistence and generalizability of improvements. This may not be surprising given the wide variety of cognitive remediation approaches and formats that have been used 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; Pentaraki et al. 2017; Reeder et al. 2016; Wykes et al. 2011). There are also no clear-cut factors that are predictive of whether cognitive improvement will occur (Reser et al. 2019), which makes it difficult to determine how to target the intervention to individuals who are most likely to respond. Nevertheless, cognitive remediation does seem to result in improvements in cognition in individuals with schizophrenia at least on a short-term basis (Harvey et al. 2018; Revell et al. 2015).

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Cognitive Remediation

- **Magnitude of effect:** *Weak*. Small but significant effects are seen for core illness symptoms and negative symptoms as well as for cognitive processes in some domains. However, significant heterogeneity is present in the degree of benefit as well as its persistence and generalizability.
- **Risk of bias:** *Medium*. RCTs, including those in systematic reviews, have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. Multiple different approaches to delivering cognitive remediation are used in the clinical trials. In addition, the use of cognitive remediation remains limited outside of research settings, which makes it difficult to compare the study methods to current practice.
- **Directness:** *Direct*. Studies measure core illness symptoms, functioning, quality of life, and treatment discontinuation as well as cognitive effects.
- **Consistency:** *Consistent*. Within each outcome, study findings were consistent.
- **Precision:** *Imprecise*. Confidence intervals are relatively wide for many outcomes.
- **Dose-response relationship:** *Not assessed*. It is not clear whether using a different frequency or duration of cognitive remediation sessions will affect outcomes.
- **Confounding factors:** *Present*. Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Not suspected*. Based on analyses conducted as part of meta-analyses on cognitive remediation, there is no evidence of publication bias.
- **Overall strength of research evidence:** *Low*. Ratings of the strength of evidence are low for global, social, and occupational function and moderate for core illness symptoms and negative symptoms. There is significant variability in the findings, perhaps related to the many differences in the study populations and treatment-related characteristics. Nevertheless, this reduces confidence in conclusions related to cognitive remediation.

Grading of the Overall Supporting Body of Research Evidence for Harms of Cognitive Remediation

Harms of cognitive remediation were not systematically studied and no grading of the evidence for harms is possible.

Statement 23: Social Skills Training

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). 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 six 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 six 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.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Social Skills Training

- **Magnitude of effect:** *Weak*. A modest effect of social skills training was noted on social function, core illness symptoms, and negative symptoms.
- **Risk of bias:** *Medium*. Studies are RCTs with a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, many of the trials also include individuals with other diagnoses. Typically, individuals also had decreases in social functioning.
- **Directness:** *Direct*. Studies measure social functioning, core illness symptoms, negative symptoms, relapse, and ability to maintain 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.

- **Consistency:** *Variable.* Findings in the three included studies are consistent for negative symptom improvements but inconsistent for improvements in functioning and core illness symptoms.
- **Precision:** *Imprecise.* Confidence intervals for some outcomes cross the threshold for clinically significant benefit of the intervention in some studies.
- **Dose-response relationship:** *Not assessed.*
- **Confounding factors:** *Present.* Confounding factors may increase the observed effect. Subjects and treating clinicians are aware of the treatment arm to which subjects were assigned. This may cause confounding of effects due to expectancies.
- **Publication bias:** *Not suspected.* A meta-analysis conducted subsequent to the AHRQ review showed no significant publication bias for studies of social skills training (Turner et al. 2018).
- **Overall strength of research evidence:** *Low.* Available RCTs have medium risk of bias, variable consistency, and lack precision, reducing the strength of the evidence.

Grading of the Overall Supporting Body of Research Evidence for Harms of Social Skills Training
Harms of social skills training were not systematically studied and no grading of the evidence for harms is possible.

Statement 24: Supportive Psychotherapy

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.

Grading of the Overall Supporting Body of Research Evidence for Efficacy of Supportive Psychotherapy

- **Magnitude of effect:** *Not present.* Based on a small number of studies there is no difference from usual care on global functioning or treatment discontinuation.

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- **Risk of bias:** *Medium*. Studies are RCTs that have a medium risk of bias based on their descriptions of randomization, blinding procedures, and study dropouts.
- **Applicability:** The included trials all involve individuals with schizophrenia. However, some trials also include individuals with other diagnoses. There is significant variation in the duration and frequency of treatment; however, variability in the delivery of supportive psychotherapy is also common in usual clinical practice.
- **Directness:** *Direct*. Studies measure functioning, core symptoms, negative symptoms, relapse, quality of life, and treatment discontinuation.
- **Consistency:** *Consistent*. For outcomes that are studied in more than one trial, findings are generally consistent.
- **Precision:** *Imprecise*. Confidence intervals are wide and cross the threshold for clinically significant benefit of the intervention for many outcomes.
- **Dose-response relationship:** *Not assessed*.
- **Confounding factors:** Unclear. Supportive therapy is similar to the type of therapy that is commonly delivered in usual care, so expectancy effects of receiving a novel intervention are likely to be minimal.
- **Publication bias:** *Unable to be assessed*. The number of studies on supportive therapy is too small to be able to assess for the presence or absence of publication bias.
- **Overall strength of research evidence:** *Low*. The overall strength of evidence is low for global functioning and study discontinuation. There is insufficient evidence to draw conclusions about other outcomes. The available trials vary in their sample sizes. Study designs also differ, which makes comparison of findings difficult.

Grading of the Overall Supporting Body of Research Evidence for Harms of Supportive Psychotherapy
 Harms of supportive psychotherapy were not systematically studied and no grading of the evidence for harms is possible.

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

Pharmacological Treatment

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Social Functioning	Olanzapine, risperidone, quetiapine immediate-release	1 SR (2 RCTs; N=343, 1 observational study; N=9,028)	Moderate Observational evidence: Moderate	Inconsistent Observational evidence: Unknown	Direct Observational evidence: Direct	Imprecise Observational evidence: Precise	Inconclusive: RCT 1: no significant differences on RFS or the SAS-SMI RCT 2: change on SFS greater with olanzapine (+7.75) than risperidone (-0.92, p=0.0028) Socially active: OR 1.27 (1.05 to 1.54); olanzapine 84.6% vs. risperidone 82.4%	Insufficient
Social Functioning	Paliperidone monthly LAI vs. risperidone biweekly LAI	1 SR (2 RCTs; N=452)	Moderate	Inconsistent	Direct	Precise	No statistically significant differences in PSP scale Mean change from baseline: 16.8 paliperidone and 18.6 risperidone; least square means difference 0.5 (-2.14 to 3.12)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Social Functioning	Paliperidone extended release vs. olanzapine	1 Meta-analysis of selected studies	High	Unknown	Direct	Precise	No significant difference in PSP scale: mean change 7.8 to 12.2 in paliperidone dose groups vs. 8.7 in olanzapine group	Insufficient
Social Functioning	Risperidone LAI vs. quetiapine immediate release	1 RCT; N=666	Moderate	Unknown	Direct	Precise	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<0.0001).	Low
Employment Outcomes	Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)	1 SR (2 RCTs, 3 observational studies; N=1,379)	Low Observational evidence: Moderate	Inconsistent Observational evidence: Consistent	Direct Observational evidence: Direct	Imprecise Observational evidence: Imprecise	No significant differences in rates of employment (mean 18% in CATIE Phase I)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Employment	Haloperidol vs. risperidone	1 SR (1 RCT; N=100)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion of patients with economic independence: RR 0.94 (0.68 to 1.29)	Insufficient
Function: Employment	Perphenazine vs. olanzapine	1 SR (1 RCT; N=597)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.29 (0.70 to 2.38)	Insufficient
Function: Employment	Perphenazine vs. quetiapine	1 SR (1 RCT; N=598)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.75 (0.90 to 3.43)	Insufficient
Function: Employment	Perphenazine vs. risperidone	1 SR (1 RCT; N=602)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.38 (0.74 to 2.57)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Employment	Perphenazine vs. ziprasidone	1 SR (1 RCT; N=446)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.22 (0.60 to 2.51)	Insufficient
Occupation and Residential Status	Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)	1 SR (21 RCT; N=771)	Moderate	Unknown	Direct	Imprecise	Inconclusive: 75.5% and 75.3% had stable status, 3.8% and 3.1% had improved status (NS)	Insufficient
Global Functioning (GAF)	Olanzapine vs. Risperidone	1 SR (4 cohort studies; N=3,211)	High	Inconsistent	Direct	Precise	No difference: Pooled WMD 0.61 (-1.78 – 2.99), I ² =43%	Low
Global Functioning (GAF)	Olanzapine vs. Quetiapine	1 SR (2 RCTs; N=363)	Moderate	Consistent	Direct	Imprecise	Pooled WMD 1.14 (-4.75 to 7.02); Q=3.99, df=1, p=0.045	Low
Function: General	Haloperidol vs. olanzapine	1 SR (1 RCT; N=208)	Moderate	Unknown	Direct	Imprecise	Inconclusive: GAF effect estimate: -4.00 (-13.70 to 5.70)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Encounters with Legal System	Haloperidol vs. olanzapine	1 SR (1 RCTs; N=31)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Encounters with legal system: RR 3.20 (0.76 to 13.46)	Insufficient
Quality of Life	Olanzapine vs. risperidone	1 SR (2 RCTs; N=492)	Moderate	Consistent	Direct	Precise	QLS Change: 7 months 13.4 vs. 8.8 (p>0.074); 12 months 0.19 vs. 0.26 (p=0.53)	Moderate
Quality of Life	Olanzapine vs. ziprasidone	1 SR (2 RCTs; N=740)	Moderate	Consistent	Direct	Precise	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)	Moderate
Quality of Life	Olanzapine vs. quetiapine immediate release	1 SR (1 RCT; N=227)	Low	Unknown	Direct	Imprecise	QLS Change: 12 months 0.19 vs. 0.09 (p>0.05)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Olanzapine vs. asenapine	1 SR (1 RCT; N=464)	Moderate	Unknown	Direct	Imprecise	QLS Change: 12 months 11.7 vs. 11.8 and 11.1 vs. 7.1 (multi-country study reported by hemisphere; p=NS)	Insufficient
Quality of Life	Olanzapine vs. clozapine	1 SR (1 RCT; N=114)	Moderate	Unknown	Direct	Imprecise	SWN scale: at 26 weeks, olanzapine found non-inferior to clozapine; difference 3.2 (4.2 to 10.5)	Insufficient
Quality of Life	Risperidone vs. ziprasidone	1 SR (N=154)	Low	Unknown	Direct	Imprecise	QLS Change: 12 months 0.19 vs. 0.26 (p>0.05)	Low
Quality of Life	Risperidone vs. quetiapine	1 SR (1 RCT; N=189)	Low	Unknown	Direct	Imprecise	QLS Change: 12 months 0.26 vs. 0.26 (p>0.05)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Quetiapine extended release vs. risperidone	1 RCT; N=798	Moderate	Unknown	Direct	Imprecise	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	Insufficient
Quality of Life	Aripiprazole oral vs. aripiprazole LAI (monthly)	1 RCT; N=724	Moderate	Unknown	Direct	Precise	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)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Aripiprazole LAI vs. paliperidone palmitate LAI (monthly)	1 RCT; N=295	Moderate	Unknown	Direct	Imprecise	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	Insufficient
Quality of Life	Risperidone LAI vs. quetiapine	1 RCT; N=666	Moderate	Unknown	Direct	Precise	SF-12 physical and mental component scores and SQLS-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 SQLS-R4, p=NR).	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Haloperidol vs. olanzapine	1 SR (5 RCTs; N=816)	Moderate	Consistent	Direct	Precise	Inconclusive: Effect sizes ranged from -3.62 to 0 using different measures; CIs were not significant	Moderate
Quality of Life	Haloperidol vs. quetiapine	1 SR (1 RCT; N=207)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Effect estimate 0.00 (-1.38 to 1.38)	Insufficient
Quality of Life	Haloperidol vs. risperidone	1 SR (2 RCTs; N=352)	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: Effect estimates ranged from -0.10 to 0.10; CIs were not significant	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Haloperidol vs. ziprasidone	1 SR (2 RCTs; N=784)	High	Inconsistent	Direct	Imprecise	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 MANSA: effect estimate -0.10 (-1.48 to 1.28)	Low
Quality of Life	Perphenazine vs. aripiprazole	1 SR (1 RCT; N=300)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with 20% improvement: RR 4.74 (2.58 to 8.69)	Insufficient
Quality of Life	Perphenazine vs. olanzapine	1 SR (1 RCT; N=597)	Moderate	Unknown	Direct	Precise	No difference: Effect estimate 0.00 (-0.16 to 0.16)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Perphenazine vs. quetiapine	1 SR (1 RCT; N=598)	Moderate	Unknown	Direct	Precise	No difference: Effect estimate 0.10 (-0.07 to 0.27)	Low
Quality of Life	Perphenazine vs. risperidone	1 SR (1 RCT; N=602)	Moderate	Unknown	Direct	Precise	No difference: Effect estimate -0.07 (-0.24 to 0.10)	Low
Quality of Life	Perphenazine vs. ziprasidone	1 SR (1 RCT; N=446)	Moderate	Unknown	Direct	Precise	No difference: Effect estimate -0.07 (-0.27 to 0.13)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Response	Network meta-analysis of olanzapine, risperidone, quetiapine immediate release, aripiprazole, clozapine, ziprasidone, asenapine, paliperidone, aripiprazole LAI monthly, caripramine, brexpiprazole, lurasidone	46 RCTs; N=12,536	Moderate	Consistent	Indirect	Precise	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.	Low
Response	Fluphenazine vs. olanzapine	1 SR (1 RCT; N=60)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.74 (0.51 to 1.07)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Response	Fluphenazine vs. quetiapine	1 SR (1 RCT; N=25)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.62 (0.12 to 3.07)	Insufficient
Response	Fluphenazine vs. risperidone	1 SR (1 RCT; N=26)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.67 (0.13 to 3.35)	Insufficient
Response	Haloperidol vs. aripiprazole	1 SR (5 RCTs; N=2,185)	Moderate	Inconsistent	Direct	Precise	No difference: RR 1.01 (0.76 to 1.34), I ² =83%	Low
Response	Haloperidol vs. asenapine	1 SR (1 RCT; N=335)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.82 (0.64 to 1.04)	Insufficient
Response	Haloperidol vs. clozapine	1 SR (2 RCTs; N=144)	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: RR 0.64 (0.28 to 1.47), I ² =72%	Insufficient
Response	Haloperidol vs. olanzapine	1 SR (14 RCTs; N=4,099)	Moderate	Inconsistent	Direct	Precise	Favors olanzapine: RR 0.86 (0.78 to 0.96), I ² =55%	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Response	Haloperidol vs. quetiapine	1 SR (6 RCTs; N=1,421)	Moderate	Inconsistent	Direct	Precise	No difference: RR 0.99 (0.76 to 1.30), I ² =77%	Low
Response	Haloperidol vs. risperidone	1 SR (16 RCTs; N=3,452)	Moderate	Consistent	Direct	Precise	No difference: RR 0.94 (CI 0.87 to 1.02), I ² =29%	Moderate
Response	Haloperidol vs. ziprasidone	1 SR (6 RCTs; N=1,283)	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: RR 0.98 (0.74 to 1.30), I ² =80%	Low
Response	Perphenazine vs. aripiprazole	1 SR (1 RCT; N=300)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.95 (0.64 to 1.40)	Insufficient
Remission	Haloperidol vs. clozapine	1 SR (1 RCT; N=71)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.16 (0.02 to 1.20)	Insufficient
Remission	Haloperidol vs. olanzapine	1 SR (3 RCTs; N=582)	Moderate	Consistent	Direct	Imprecise	Favors olanzapine: RR 0.65 (0.45 to 0.94), I ² =54%	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Remission	Haloperidol vs. quetiapine	1 SR (1 RCT; N=207)	High	Unknown	Direct	Imprecise	Inconclusive: RR 0.72 (0.41 to 1.25)	Insufficient
Remission	Haloperidol vs. risperidone	1 SR (2 RCTs; N=179)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 0.84 (0.56 to 1.24), I ² =0%	Low
Remission	Haloperidol vs. ziprasidone	1 SR (3 RCTs; N=1,085)	High	Consistent	Direct	Precise	No difference: RR 0.89 (0.71 to 1.12), I ² = 12%	Low
Mortality (All-Cause)	Olanzapine vs. risperidone vs. quetiapine	1 SR (1 retrospective cohort study; N=48,595)	Low	Unknown	Direct	Precise	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).	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Mortality (All-Cause)	Clozapine, risperidone, olanzapine and quetiapine vs. no treatment	1 SR (1 retrospective cohort study; N=6,987)	Low	Unknown	Direct	Imprecise	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.	Insufficient
Mortality (All-Cause)	Asenapine vs. olanzapine	2 RCTs; N=2,174 (1 RCT reported 2 RCT studies)	Moderate	Consistent	Direct	Imprecise	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)	Low
Mortality (All-Cause)	Paliperidone palmitate LAI (monthly) vs. risperidone LAI	2 RCTs; N=752	Moderate	Consistent	Direct	Imprecise	Inconclusive: RCT 1: 0.79% vs. 0.27% RCT 2: 0% vs. 0.45% RR 1.26 (0.21 to 7.49)	Low
Mortality (All-Cause)	Quetiapine vs. risperidone	2 RCTs; N=1,057	Moderate	Consistent	Direct	Imprecise	Inconclusive: RCT 1: 1.17% vs. 0.40% RCT 2: 0.72% vs. 0% RR 3.24 (0.72 to 14.6)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Cardio-vascular Mortality	Olanzapine vs. risperidone vs. quetiapine	1 SR (2 retrospective cohort study; N=55,582)	Low	Consistent	Direct	Precise	No significant differences between the drugs: HRs 0.99 (0.37 to 2.67) and 0.76 (0.25 to 2.28), respectively	Low
Cardio-vascular Mortality	Clozapine vs. risperidone	1 SR (2 retrospective cohort studies; N=1,686)	Moderate	Unknown	Direct	Imprecise	Inconclusive: No significant differences between drugs: 4.8% vs. 2.5%; RR 1.39 (0.61 to 2.53)	Insufficient
Self-Harm: Suicidal Behavior, Suicide	Clozapine vs. olanzapine in high-risk patients	1 SR (1 RCT; N=980)	Low	Unknown	Direct	Imprecise	Suicidal behavior: HR 0.76 (0.58 to 0.97)	Low
Self-Harm: Suicidal Behavior, Suicide	Clozapine vs. olanzapine in high-risk patients	1 SR (1 RCT; N=980)	Low	Unknown	Direct	Precise	Worsening on CGI-Suicide Severity: HR 0.78 (0.61 to 0.99)	Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Self-Harm: Suicidal Behavior, Suicide	Clozapine vs. olanzapine in high-risk patients	1 SR (1 RCT; N=980)	Low	Unknown	Direct	Imprecise	Suicide deaths: No significant differences (5 clozapine, 3 olanzapine)	Low
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR (2 retrospective cohorts; N=16,584)	Moderate	Consistent	Direct	Precise	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	Low
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR (1 prospective cohort; N=10,204)	High	Unknown	Direct	Precise	Suicide attempts (6 months): No statistically significant difference between drugs	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR (1 prospective cohort; N=20,489)	High	Unknown	Direct	Precise	Inconclusive: Suicide attempts or death by suicide: aripiprazole vs. all others combined HR 0.69 (0.42 to 1.14)	Insufficient
Reduction in Self Harm	Haloperidol vs. olanzapine	1 SR (1 RCT; N=182)	Moderate	Unknown	Indirect	Imprecise	Inconclusive: Attempted suicide: RR 3.13 (0.13 to 76) Completed suicide: RR 3.13 (0.13 to 76)	Insufficient
Reduction in Self Harm	Perphenazine vs. olanzapine	1 SR (1 RCT; N=597)	Moderate	Unknown	Indirect	Imprecise	Inconclusive: Attempted suicide: RR 0.64 (0.06 to 7.06) Completed suicide: RR 3.86 (0.40 to 37)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Core Illness Symptoms	Oral SGAs (except caripramine): meta-analysis of clozapine, amisulpride, olanzapine, risperidone, paliperidone, zotepine, haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, lurasidone, and iloperidone	212 RCTs; N=43,049	Moderate	Consistent	Indirect	Precise	<p>Clozapine had significantly better improvement than the other drugs except olanzapine: SMDs on PANSS or BPRS -0.32 to -0.55.</p> <p>Olanzapine and risperidone superior to the other drugs, except for each other and paliperidone: SMDs -0.13 to -0.26.</p> <p>Paliperidone superior to lurasidone and iloperidone: SMD -0.17.</p> <p>All drugs superior to placebo: SMDs -0.33 to -0.88.</p>	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Core Illness Symptoms	Treatment resistant patients: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone	Network meta-analysis (40 RCTs; N=5,172)	Moderate	Consistent	Indirect	Precise	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)	Low
Core Illness Symptoms	Brexpiprazole vs. aripiprazole	1 open label study; N=97	Moderate	Unknown	Indirect	Imprecise	Inconclusive: PANSS: least square means difference -22.9 vs. -19.4 at 6 weeks from baseline; direct comparison not reported.	Insufficient
Overall/Any Adverse Events	Asenapine vs. olanzapine	5 RCTs (4 publications; N=2,189)	Moderate	Consistent	Direct	Precise	Pooled RR 1.00 (0.96 to 1.05), I ² =9%	Moderate
Overall/Any Adverse Events	Quetiapine vs. risperidone	7 RCTs; N=3,254	Moderate	Consistent	Direct	Precise	Pooled RR 1.04 (0.97 to 1.12), I ² =56%	Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Overall/Any Adverse Events	Clozapine vs. olanzapine	2 RCTs; N=182	Moderate	Consistent	Direct	Imprecise	Pooled RR 1.15 (1.00 to 1.33), I ² =0%	Low
Overall/Any Adverse Events	Risperidone vs. olanzapine	5 RCTs; N=873	Moderate	Inconsistent	Direct	Precise	Pooled RR 1.02 (0.81 to 1.29), I ² =77%	Low
Overall/Any Adverse Events	Olanzapine vs. ziprasidone	5 RCTs; N=1,097 (6 weeks to 6 months durations)	Moderate	Inconsistent	Direct	Precise	Pooled RR 1.00 (0.86 to 1.16), I ² =80%	Low
Overall/Any Adverse Events	Olanzapine vs. quetiapine	3 RCTs; N=448	Moderate	Consistent	Direct	Imprecise	Pooled RR 0.90 (0.74 to 1.11), I ² =30%	Low

Overall/Any Adverse Events	<p>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</p>	1 SR (28 RCTs; N=7,810)	Moderate	Consistent	Direct	Imprecise	No statistically significant differences were found in each comparison.	Low
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Overall/Any Adverse Events	Oral aripiprazole vs. brexpiprazole, olanzapine, paliperidone, and risperidone LAI; ziprasidone vs. clozapine, risperidone, iloperidone and lurasidone; risperidone vs. asenapine, caripramine 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.	1 SR (31 RCTs; N=6,700)	Moderate	Unknown	Direct	Imprecise	No statistically significant differences were found in single studies of each comparison.	Insufficient
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Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Overall Adverse Events	Haloperidol vs. aripiprazole	1 SR (3 RCTs; N=1,713)	Moderate	Consistent	Direct	Precise	RR 1.11 (1.06 to 1.17), I ² =0%; less with aripiprazole	Moderate
Overall Adverse Events	Haloperidol vs. risperidone	1 SR (8 RCTs; N=1,313)	Moderate	Consistent	Direct	Precise	RR 1.20 (1.01 to 1.42), I ² =84%; less with risperidone	Moderate
Overall Adverse Events	Haloperidol vs. ziprasidone	1 SR (6 RCTs; N=1,448)	Moderate	Consistent	Direct	Precise	RR 1.13 (1.03 to 1.23), I ² =31%; less with ziprasidone	Moderate

Discontinuation Due to Adverse Events	Network meta-analysis of aripiprazole, aripiprazole monthly LAI, asenapine, brexipiprazole, cariprazine, clozapine, iloperidone, lurasidone ¹⁰ , 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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Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
							ziprasidone (OR 0.59, 95% CI 0.43 to 0.84). 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).	
Withdrawal Due to Adverse Events	Fluphenazine vs. olanzapine	1 SR (1 RCT; N=60)	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 0.74 (0.51 to 1.07)	Insufficient
Withdrawal Due to Adverse Events	Fluphenazine vs. quetiapine	1 SR (1 RCT; N=25)	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 0.19 (0.01 to 3.52)	Insufficient
Withdrawal Due to Adverse Events	Haloperidol vs. asenapine	1 SR (1 RCT; N=335)	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 1.53 (0.74 to 3.16)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Withdrawal Due to Adverse Events	Haloperidol vs. aripiprazole	1 SR (7 RCTs) plus 1 additional RCT; N=3,232	Moderate	Consistent	Direct	Precise	RR 1.25 (1.07 to 1.47), I ² =0%	Moderate
Withdrawal Due to Adverse Events	Haloperidol vs. clozapine	1 SR (5 RCTs; N=719)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.00 (0.66 to 1.50), I ² =0%	Low
Withdrawal Due to Adverse Events	Haloperidol vs. olanzapine	1 SR (21 RCTs) plus 3 RCTs; N=5,708	Moderate	Consistent	Direct	Precise	RR 1.89 (1.57 to 2.27), I ² =0%	Moderate
Withdrawal Due to Adverse Events	Haloperidol vs. quetiapine	1 SR (8 RCTs) plus 2 RCTs; N=1,759	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.97 (0.96 to 4.01), I ² =62%	Low
Withdrawal Due to Adverse Events	Haloperidol vs. risperidone	1 SR (23 RCTs) plus 2 RCTs; N=4,581	Moderate	Consistent	Direct	Precise	RR 1.32 (1.09 to 1.60), I ² =0%	Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Withdrawal Due to Adverse Events	Haloperidol vs. ziprasidone	1 SR (6 RCTs) plus 1 RCT; N=1,597	Moderate	Consistent	Direct	Precise	RR 1.68 (1.26 to 2.23), I ² =0%	Moderate
Withdrawal Due to Adverse Events	Perphenazine vs. aripiprazole	1 SR (1 RCT; N=300)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.53 (0.27 to 1.05)	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. olanzapine	1 SR (1 RCT; N=597)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.83 (0.58 to 1.19)	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. quetiapine	1 SR (1 RCT; N=598)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.05 (0.72 to 1.55)	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. risperidone	1 SR (1 RCT; N=602)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.54 (1.00 to 2.36)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Withdrawal Due to Adverse Events	Perphenazine vs. ziprasidone	1 SR (1 RCT; N=446)	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.01 (0.65 to 1.58)	Insufficient

Abbreviations: 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; MANSA=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

Assertive Community Treatment

Outcome	Comparators	Number of studies Number of subjects	study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function	Assertive community treatment vs. usual care	1 SR (3 RCTs) plus 1 RCT; N=118	Moderate	Consistent	Direct	Imprecise	No difference in social function compared with usual care. Social function: mean difference 0.03 (-0.28 to 0.34)	Low
Trouble with Police	Assertive community treatment vs. usual care	1 SR (4 RCTs)	Moderate	Consistent	Direct	Imprecise	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)	Low

Outcome	Comparators	Number of studies Number of subjects	study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Housing and Independent Living	Assertive community treatment vs. usual care	1 SR (3 RCTs) plus 1 RCT; N=118	Moderate	Consistent	Direct	Precise	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).	Moderate
Employment	Assertive community treatment vs. usual care	1 SR (3 RCTs)	Moderate	Consistent	Direct	Precise	Less likely to be unemployed (OR 0.46, 95% CI 0.21 to 0.99)	Moderate
Quality of Life	Assertive community treatment vs. usual care	1 SR (1 RCT; N=125) plus 1 RCT; N=118	Moderate	Inconsistent	Direct	Imprecise	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.	Insufficient

Outcome	Comparators	Number of studies Number of subjects	study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Overall Symptoms	Assertive community treatment vs. usual care	1 SR (3 RCTs) plus 1 RCT; N=118	Moderate	Consistent	Direct	Precise	No differences were found in 4 trials (mean difference -0.14, 95% CI -0.36 to 0.08).	Moderate
Treatment Maintenance (Loss to follow-up)	Assertive community treatment vs. usual care	1 SR (10 RCTs) plus 1 RCT; N=118	Moderate	Consistent	Direct	Precise	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)	Moderate

Abbreviations: CI=confidence interval; OR=odds ratio; RCT=randomized controlled trial; SR=systematic review

Cognitive-behavioral Therapy

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Function: Global Function – Short term (≤6 months since CBT initiation)	CBT vs. usual care	1 SR (3 RCTs) plus 5 RCTs; N=701	Moderate	Consistent	Direct	Precise	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)	Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Function: Global Function – Medium term (>6 months to 1 year since CBT initiation)	CBT vs. usual care	3 RCTs; N=465	Moderate	Inconsistent	Direct	Imprecise	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	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Function: Global Function – Long term (>1 year since CBT initiation)	CBT vs. usual care	1 SR (4 RCTs) plus 4 RCTs; N=851	Moderate	Consistent	Direct	Imprecise	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.	Low
Function: Basic Living Skills	CBT vs. usual care	1 RCT; N=76	Moderate	Unknown	Direct	Imprecise	No difference between groups.	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Function: Employment Outcomes	CBT vs. usual care	2 RCTs; N=522	Moderate	Inconsistent	Direct	Imprecise	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	Insufficient
Quality of Life	CBT vs. usual care	12-24 weeks follow-up; 2 RCTs; N=216	Moderate	Consistent	Direct	Imprecise	CBT led to improved quality of life 0 and 16 weeks after cessation of treatment based on CHOICE, WEMWEBS, and WHOQOL-BREF scales.	Low
Quality of Life	CBT vs. usual care	18 to 24 months follow-up; 2 RCTs; N=489	Moderate	Consistent	Direct	Imprecise	CBT not different from usual care based on WHOQOL and EROQOL scales	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Suicide and Suicidality	CBT vs. usual care	2 RCTs; N=307	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 0.68 (0.12 to 3.93) and RR 0.53 (0.12 to 2.79)	Insufficient
Core Illness Symptoms	CBT vs. usual care	1 SR (34 RCTs; N=2,989)	Moderate	Consistent	Direct	Precise	SMD -0.33 (0.47 to -0.19); subgroup with outcome assessment blinding SMD -0.15 (-0.27 to -0.03)	Moderate
Negative Symptoms	CBT vs. usual care	2 SRs (34 RCTs; N=3,393)	Moderate	Inconsistent	Direct	Precise	SMD -0.13 (-0.25 to -0.01), I ² =48% (in this review a negative estimate favors CBT); and SMD 0.09 (-0.03 to 0.21), I ² =63% (in this review, a positive estimate favors CBT)	Low
Ability to Maintain Treatment	CBT vs. usual care	13 RCTs; N=1,847	Moderate	Inconsistent	Direct	Precise	No difference: RR 1.03 (0.96 to 1.10), I ² =64%	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of Evidence (high, moderate, low, insufficient)
Relapse	CBT vs. usual care	6 RCTs; N=1,090	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: RR 0.80 (0.51 to 1.25), I ² =77% Sub-analysis limited to relapse defined as "hospitalization" (3 RCTs): 0.70 (0.54 to 0.91), I ² =0%	Insufficient
Harms	CBT vs. usual care	1 RCT; N=150	Moderate	Inconsistent	Direct	Imprecise	None of the adverse events were related to treatment: 2 vs. 4 suicide attempts; 1 vs. 1 serious violent incident	Insufficient

Abbreviations: 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

Cognitive Remediation

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function	Cognitive remediation vs. usual care	1 SR (19 RCTs) plus 3 RCTs; N=1,323	Moderate	Consistent	Direct	Imprecise	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).	Low
Quality of life	Cognitive remediation vs. usual care	1 RCT; N=69	Moderate	Unknown	Direct	Imprecise	Quality of life was only reported in one trial, with no difference between cognitive remediation and usual care.	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Overall symptoms	Cognitive remediation vs. usual care	2 RCTs; N=153	Moderate	Consistent	Direct	Imprecise	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).	Moderate
Negative symptoms	Cognitive remediation vs. usual care	1 SR (18 RCTs; N=781)	Moderate	Consistent	Direct	Precise	Negative symptoms improved more in cognitive remediation groups: effect size -0.36 (-0.52 to -0.20); a negative effect size favors cognitive remediation.	Moderate
Ability to maintain treatment	Cognitive remediation vs. usual care	3 RCTs; N=302	Moderate	Consistent	Direct	Imprecise	There was no difference in ability to maintain treatment in three RCTs of cognitive remediation	Low

Abbreviations: CI=confidence interval; RCT=randomized controlled trial; SMD=standard mean difference; SR=systematic review

Family Interventions

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Occupational (Unemployed) -1 year	Family intervention vs. usual care	1 SR (4 RCTs; N=230)	Moderate	Consistent	Direct	Imprecise	RR 1.09 (0.92 to 1.29)	Low
Function: Occupational (Unemployed) – 2 years	Family intervention vs. usual care	1 SR (1 RCT; N=51)	Moderate	Unknown	Direct	Imprecise	RR 1.33 (0.84 to 2.10)	Insufficient
Function: Occupational (Unemployed) – 3 years	Family intervention vs. usual care	1 SR (1 RCT; N=99)	Moderate	Unknown	Direct	Imprecise	RR 1.19 (0.92 to 1.55)	Insufficient
Function: Living situation (cannot live independently) – 1 year	Family intervention vs. usual care	1 SR (3 RCTs; N=164)	Moderate	Consistent	Direct	Imprecise	RR 0.83 (0.66 to 1.03)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Living situation (cannot live independently) - 3 years	Family intervention vs. usual care	1 SR (1 RCT; N=99)	Moderate	Unknown	Direct	Imprecise	RR 0.82 (0.59 to 1.14)	Insufficient
Function: Living situation (cannot live independently, months in psychiatric facility) - 5 years	Family intervention vs. usual care	1 RCT; N=73	Moderate	Unknown	Direct	Imprecise	10.87 vs. 21.18 months, p=0.04	Insufficient
Social Functioning	Family intervention vs. usual care	1 RCT; N=69	Moderate	Unknown	Direct	Imprecise	No between group differences	Insufficient
Quality of Life	Family intervention vs. usual care	1 SR (1 RCT; N=50) plus one RCT not in SR; N=55	Moderate	Unknown	Direct	Imprecise	Heinrichs scale: MD -5.05 (-15.44 to 5.34) EUROQOL: MD -7.38 (-22.07 to 7.31)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Depression	Family intervention vs. usual care	2 RCTs; N=124	Moderate	Consistent	Direct	Imprecise	RCT 1, 6 months: -1.0 (-12 to 22) vs. 0 (-15 to 17) RCT 1, 12 months: 3.0 (-15 to 17) vs. 0 (-14 to 17) RCT 2, 12 months; 3.35 (-2.64 to 9.34) RCT 2, 24 months: -0.11 (-6.91 to 6.68)	Low
Anxiety	Family intervention vs. usual care	1 RCT; N=55	Low	Unknown	Direct	Imprecise	12 months: -0.42 (-6.97 to 6.13) 24 months: -2.36 (-9.13 to 4.40)	Insufficient
Suicide	Family intervention vs. usual care	1 SR (6 RCTs; N=314)	Moderate	Consistent	Direct	Imprecise	RR 0.85 (0.24 to 3.02)	Low
Core Illness Symptoms:	Family intervention vs. usual care	1 SR (2 RCTs; N=223)	Moderate	Consistent	Direct	Imprecise	SMD -0.46 (-0.73 to -0.20)	Low
Negative Symptoms	Family intervention vs. usual care	3 RCTs; N=163	Moderate	Consistent	Direct	Imprecise	SMD -0.38 (-0.69 to -0.07)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Leaving the study early (3-6 months)	Family intervention vs. usual care	1 SR (6 RCTs; N=504)	Moderate	Consistent	Indirect	Imprecise	RR 0.86 (0.50 to 1.47)	Low
Leaving the study early (7-12 months)	Family intervention vs. usual care	1 SR (9 RCTs; N=487) plus 4 RCTs; N=466	Moderate	Consistent	Indirect	Imprecise	RR 0.77 (0.64 to 0.93)	Low
Leaving the study early (13-24 months)	Family intervention vs. usual care	1 SR (6 RCTs; N=362)	Moderate	Consistent	Indirect	Imprecise	RR 0.82 (0.57 to 1.16)	Low
Leaving the study early (25-36 months)	Family intervention vs. usual care	1 SR (2 RCTs; N=90)	High	Consistent	Indirect	Imprecise	RR 0.59 (0.24 to 1.49)	Insufficient
Leaving the study early after 3 years	Family intervention vs. usual care	1 SR (1 RCT; N=63)	Moderate	Unknown	Indirect	Imprecise	RR 1.72 (0.71 to 4.16)	Insufficient
Poor compliance with medication	Family intervention vs. usual care	1 SR (4 RCTs; N=174) plus 2 RCTs; N=256	Moderate	Consistent	Indirect	Imprecise	RR 0.78 (0.65 to 0.92)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Relapse 0-6 months	Family intervention vs. usual care	1 SR (2 RCTs; N=167)	Moderate	Consistent	Direct	Imprecise	RR 0.62 (0.41 to 0.92)	Low
Relapse (7-12 months)	Family intervention vs. usual care	1 SR ⁵⁹ (16 RCTs; N=861) plus 4 RCTs; N=314	Moderate	Consistent	Direct	Imprecise	RR 0.67 (0.54 to 0.83)	Moderate
Relapse (13-24 months)	Family intervention vs. usual care	1 SR5 (9 RCTs; N=517)	Moderate	Consistent	Direct	Imprecise	RR 0.75 (0.58 to 0.99)	Low
Relapse (25-36 months)	Family intervention vs. usual care	1 SR (2 RCTs; N=147)	Moderate	Inconsistent	Direct	Imprecise	RR 1.05 (0.80 to 1.39)	Low
Relapse (5 years)	Family intervention vs. usual care	1 SR (1 RCT; N=63) plus 1 RCT; N=77	Moderate	Consistent	Direct	Imprecise	RR 0.82 (0.72 to 0.94)	Low
Relapse (8 years)	Family intervention vs. usual care	1 SR (1 RCT; N=62)	Moderate	Unknown	Direct	Imprecise	RR 0.86 (0.71 to 1.05)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Family Burden Not Improved or Worse	Family intervention vs. usual care	1 SR (1 RCT; N=51)	Moderate	Unknown	Direct	Imprecise	Social functioning: RR 2.40 (0.51 to 11.27) at 1 year RR 2.88 (0.64 to 12.97) at 2 years Subjective burden: RR 1.44 (0.60 to 3.46) at 1 year RR 0.58 (0.15 to 2.16) at 2 years	Insufficient
Nonsuicide mortality	Family intervention vs. usual care	1 SR (3 RCTs; N=113)	Moderate	Consistent	Direct	Imprecise	RR 0.96 (0.17 to 5.33)	Insufficient

Abbreviations: 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

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function	Intensive case management vs. usual care	1 SR (3 RCTs) 1 RCT; N=77	Moderate	Consistent	Direct	Imprecise	Inconclusive: Pooled mean difference 0.46 (-0.34 to 0.1.26); one subsequent trial also found no difference using a different scale	Low
Quality of Life	Intensive case management vs. usual care	1 SR (2 RCTs) 1 RCT; N=77	Moderate	Consistent	Direct	Imprecise	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.	Insufficient
Overall Symptoms	Intensive case management vs. usual care	1 SR (2 RCTs) 1 RCT; N=77	Moderate	Consistent	Direct	Imprecise	Inconclusive: Pooled mean difference 0.46 (-3.67 to 4.60); one subsequent trial also reported no difference.	Low
Loss to Follow-up	Intensive case management vs. usual care	1 SR (7 RCTs) 1 RCT; N=77	Moderate	Consistent	Direct	Precise	Less loss to follow-up with intensive case management compared to usual care: OR 0.70 (0.54 to 0.90)	Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Imprisonment	Intensive case management vs. usual care	1 SR (5 RCTs)	Moderate	Consistent	Direct	Imprecise	No significant differences in imprisonment: OR 0.90 (0.45 to 1.82)	Low

Abbreviations: CI=confidence interval; RCT=randomized controlled trial; OR=odds ratio; SR=systematic review

Illness Management and Recovery

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functioning	Illness self-management/ self-management education intervention vs. usual care	1 SR (10 RCTs; N=409) plus 1 RCT; N=210	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: Heterogeneous methods for measuring various types of functioning were used, with 5 finding benefit ad 6 not.	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Symptoms	Illness self-management/ self-management education intervention vs. usual care	1 SR (5 RCTs; N=409)	Moderate	Consistent	Direct	Precise	BPRS (n=409), WMD: -4.19 (-5.84 to -2.54)	Moderate
Negative Symptoms	Illness self-management/ self-management education intervention vs. usual care	1 SR (3 RCTs; N=257)	Moderate	Consistent	Direct	Imprecise	PANSS negative -4.01 (-5.23 to -2.79)	Low
Relapse	Illness self-management/ self-management education intervention vs. usual care	1 SR (3 RCTs; N=534)	Moderate	Consistent	Direct	Imprecise	Relapse (>10 interventions): N=233, OR 0.41 (0.21-0.79), p=0.008 Relapse (<10 interventions): N=269, OR 0.67 (0.39-1.15), p=0.014	Low

Abbreviations: 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

Psychoeducation

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Global Functioning (GAF/GAS) at end of intervention	Psychoeducation vs. standard care	1 SR (1 RCT; N=41)	Medium	Unknown	Direct	Imprecise	Inconclusive: MD -2.64 (-12.74 to 7.46)	Insufficient
Global Functioning (GAS) at 6 months	Psychoeducation vs. standard care	1 SR (1 RCT; N=92)	Medium	Unknown	Direct	Imprecise	Inconclusive: Risk Ratio 0.83 (0.50 to 1.38)	Insufficient
Global Functioning (GAF/GAS) at 1 year	Psychoeducation vs. standard care	1 SR (3 RCTs; N=260)	Medium	Consistent	Direct	Imprecise	MD -5.23 (-8.76 to -1.71), I ² 79%	Low
Global Functioning (GAS) at 18 months	Psychoeducation vs. standard care	1 SR (1 RCT; N=92)	Medium	Unknown	Direct	Imprecise	Inconclusive: Risk Ratio 0.90 (0.58 to 1.39)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Global Functioning (GAF/GAS) at 2 years	Psychoeducation vs. standard care	1 SR (1 RCT; N=59)	Medium	Unknown	Direct	Imprecise	MD -6.70 (-13.38 to -0.02)	Insufficient
Global Functioning (GAF/GAS) at 5 years	Psychoeducation vs. standard care	1 SR (1 RCT; N=60)	Medium	Unknown	Direct	Imprecise	Inconclusive: MD -3.80 (-8.04 to 0.44)	Insufficient
Social Functioning (SAS-II) at end of intervention	Psychoeducation vs. standard care	1 SR (1 RCT; N=19)	Medium	Unknown	Direct	Imprecise	Inconclusive: MD -0.10 (-0.37 to 0.17)	Insufficient
Quality of Life (Heinrich's Scale) at end of intervention	Psychoeducation vs. standard care	1 SR (1 RCT; N=114)	Medium	Unknown	Direct	Imprecise	MD -8.20 (-14.78 to -1.62)	Insufficient
Quality of Life (Heinrich's Scale) at 3 months	Psychoeducation vs. standard care	1 SR (1 RCT; N=108)	Medium	Unknown	Direct	Imprecise	MD -9.70 (-17.22 to -2.18)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
BPRS at 3 months	Psychoeducation vs. standard care	1 SR (1 RCT; N=19)	Medium	Unknown	Direct	Imprecise	Inconclusive: MD -0.06 (-0.53 to 0.41)	Insufficient
BPRS at 1 year	Psychoeducation vs. standard care	1 SR (1 RCT; N=159)	Medium	Unknown	Direct	Imprecise	MD -6.0 (-9.15 to -2.85)	Insufficient
Relapse with or without readmission: 9 to 18 Months		1 SR (6 RCTs; N=720)	Medium	Consistent	Direct	Precise	Risk ratio 0.80 (0.70 to 0.92), I ² 54%	Moderate
Relapse without readmission: total	Psychoeducation vs. standard care	1 SR (3 RCTs; N=385)	Medium	Consistent	Direct	Imprecise	Inconclusive: risk ratio 1.05 (0.84 to 1.31), I ² 60%	Low
Relapse Without Readmission: 1 Year	Psychoeducation vs. standard care	1 SR (2 RCTs; N=303)	Medium	Consistent	Direct	Imprecise	Inconclusive: risk ratio 1.16 (0.92 to 1.46), I ² 0.0%	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Relapse Without Readmission: 18 months	Psychoeducation vs. standard care	1 SR (1 RCT; N=382)	Medium	Unknown	Direct	Imprecise	Inconclusive: risk ratio 0.5 (0.23 to 1.11)	Insufficient
Harms: mortality	Psychoeducation vs. standard care	1 SR (2 RCTs; N=170)	Medium	Consistent	Direct	Imprecise	Inconclusive: risk ratio 0.53 (0.07 to 3.95), I ² 0.0%	Low

Abbreviations: 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

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function	Social skills training vs. usual care	3 RCTs (4 publications); N=384	Moderate	Consistent	Direct	Imprecise	Significant improvement in scale scores during treatment for 6 months to 2 years (SMD 0.65 to 1.60)	Low
Function	Social skills training vs. usual care	1 RCT; N=183	Moderate	Unknown	Direct	Imprecise	Social function not different from control after treatment cessation (1 study; SMD 0.24, 95% CI -0.05 to 0.53)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Overall Symptoms	Social skills training vs. usual care	2 RCT; N=201	Moderate	Consistent	Direct	Imprecise	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)	Low
Overall Symptoms	Social skills training vs. usual care	1 RCT; N=183	Moderate	Unknown	Direct	Imprecise	Inconclusive: Mixed population (55% schizophrenia), no significant effect on symptoms (BPRS): SMD -0.04 (-0.33 to 0.25)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Negative Symptoms	Social skills training vs. usual care	3 RCTs (4 publications); N=384	Moderate	Consistent	Direct	Imprecise	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	Low
Negative Symptoms	Social skills training vs. usual care	1 RCT; N=183	Moderate	Unknown	Direct	Imprecise	Negative symptoms were better with social skills training than usual care 1 year after treatment discontinuation: SMD -0.45 (-0.74 to -0.15)	Insufficient
Ability to Maintain Treatment	Social skills training vs. usual care	2 RCTs; N=384	Moderate	Consistent	Direct	Imprecise	No difference: 1 year: RR 1.10 (0.92 to 1.31) 2 year: RR 1.01 (0.88 to 1.16)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Relapse	Social skills training vs. usual care	1 RCT; N=82	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.50 (0.18 to 1.36)	Insufficient

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

Supported Employment

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional (occupational) - # in competitive employment	IPS vs. standard services	1 trial; N=204	Moderate	Unknown	Direct	Imprecise	75% vs. 27.5% (p<0.001)	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional (occupational) - # in competitive employment	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT; N=1,273	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care: 55% vs 34% (p<0.001) Subgroup analysis of only patients with schizophrenia: 22% vs. 12%, p<0.001 with mixed effects logistic regression	Moderate
Functional (occupational) - # in competitive employment	All comparators							Moderate
Functional (occupational) - Days to first competitive employment	IPS vs. standard services	1 trial; N=204	Moderate	Unknown	Direct	Imprecise	Days to first job: 196.63 vs. 218.84, p=0.019	Low
Functional (occupational) – Worked more than 20 hours per week	IPS vs. standard services	1 trial; N=204	Moderate	Unknown	Direct	Imprecise	Worked > 20hours per week: 33.8% vs 13%, p=0.001	Low

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional (occupational) – Worked more than 20 hours per week	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT; N=1,273	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care Working ≥ 40 hours per month: 51% vs. 39%, $p < 0.001$	Moderate
Functional (occupational) – Worked more than 20 hours per week	All comparators							Moderate
Functional (occupational) – Wages earned	IPS vs. standard services	1 trial; N=204	Moderate	Unknown	Direct	Imprecise	\$2,078/month vs. \$617.59/month, $p < 0.001$	Low
Functional (occupational) – Wages earned	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT; N=1,273	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care \$122/month vs. \$99/month, $p = 0.04$	Moderate
Functional (occupational) – Wages earned	All comparators							Moderate

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional (occupational) – Weeks worked (mean)	IPS vs. standard services	1 trial; N=204	Moderate	Unknown	Direct	Imprecise	Total weeks worked: 29.72 vs. 5.45, p<0.001	Low
Functional (occupational) – Weeks worked (mean)	Supported Employment (primarily IPS) vs. vocational training	1 SR; N=2,265	Moderate	Consistent	Indirect for this review question	Precise	Supported Employment vs. vocational training Days employed: mean difference 70.63 (43.22 to 98.04)	Moderate
Functional (occupational) – Weeks worked (mean)	All comparators							Moderate

Abbreviations: CI=confidence interval; IPS=Individual placement and support; RCT=randomized controlled trial; SR=systematic review

Supportive Therapy

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Global Functioning	Supportive therapy vs. standard care	1 SR (2 RCTs; N=289)	Moderate	Consistent	Direct	Imprecise	Inconclusive: GAF-M, n=29: MD 1.40 (-5.09 to 7.89) GAS, n=260: MD -2.66 (-6.20 to 0.88)	Low
Social Functioning	Supportive therapy vs. standard care	1 SR (1 RCT; N=260)	Moderate	Unknown	Direct	Imprecise	Inconclusive: SFS: MD -0.67 (-7.05 to 5.71)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Quality of Life	Supportive therapy vs. standard care	1 SR (1 RCT; N=260)	Moderate	Unknown	Direct	Imprecise	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)	Insufficient
Relapse	Supportive therapy vs. standard care	1 SR (1 RCT; N=54)	Moderate	Unknown	Direct	Imprecise	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)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Core Symptoms	Supportive therapy vs. standard care	1 SR (2 RCTs; N=167)	Moderate	Unknown	Direct	Imprecise	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)	Insufficient
Negative Symptoms	Supportive therapy vs. standard care	1 SR (1 RCT; N=47)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Short-term: mean 10.19 vs. 10.73; Long-term: mean 9.90 vs. 11.46 (no statistical analysis because of skewed data)	Insufficient

Outcome	Comparators	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Discontinuing Treatment	Supportive therapy vs. standard care	1 SR (4 RCTs; N=354)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 0.86 (0.53 to 1.40)	Low

Abbreviations: CI=confidence interval; GAF-M=Global Assessment Functioning modified; GAS=Global Assessment Scale; GHQ=Global Health Quotient; MD=mean difference; PANSS=Positive and Negative Syndrome Scale; RCT=randomized controlled trial; RR=relative risk; RSES=Rosenberg Self-Esteem Scale; SFS=Social Functioning Scale; SR=systematic review; WBS=Well-Being Scale

Early Interventions for Patients With First-episode Psychosis

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional: Global (GAS, GAF)	1 SR (1 RCT; N=369, two-year data only) plus 2 RCTs; N=744, N=98	Moderate	Consistent	Direct	Precise	GAS and GAF results only Team-based CSC resulted in higher functioning scores. Pooled WMD: 3.88 (0.91 to 6.85), I ² =64%	Moderate

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Functional: Working or School	1 SR (1 RCT; (OPUS-Scandinavia) N=547) plus 2 RCTs; N=744, N=125	Moderate	Consistent	Direct	Precise	Significantly more people (22%) are working or in school with team-based CSC. Pooled RR 1.22 (1.01 to 1.47)	Moderate
Functional: Housing Status	1 SR (1 RCT; N=547) plus 1 RCT; N=128	Moderate	Consistent	Direct	Imprecise	No significant difference between groups Pooled RR 1.06 (0.86 to 1.30)	Low
Health-Related Quality of Life	2 RCTs; N=92, N=403	Moderate	Consistent	Direct	Precise	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)	Moderate

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Core Illness Symptoms (PANSS)	3 RCTs; N=99, N=403, N=1,184	Moderate	Inconsistent	Direct	Precise	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	Low
Core Illness Symptoms (Calgary Depression Scale)	2 RCTs; N=99, N=205	Moderate	Consistent	Direct	Precise	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	Moderate

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Discontinuation of Treatment	2 RCTs; N=1,239, N=136	Moderate	Consistent	Direct	Precise	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	High
Rates of Relapse	2 RCTs; N=1,239, N=122	Moderate	Consistent	Direct	Imprecise	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	Moderate

Abbreviations: CI=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

Co-occurring Substance Use and Schizophrenia

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 6 months)	1 SR (1 RCT; N=162)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.10 (-1.58 to 3.78)	Low
Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 18 months)	1 SR (1 RCT; N=176)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.00 (-1.58 to 3.58)	Low
Function: Global Function (Integrated models of care vs. treatment as usual: GAF; 24 months)	1 SR (1 RCT; N=166)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.70 (-1.18 to 4.58)	Low

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Function: Global Function (Integrated models of care vs. treatment as usual: GAF: 30 months)	1 SR (1 RCT; N=164)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD -0.60 (-3.56 to 2.36)	Low
Function: Global Function (Integrated models of care vs. treatment as usual: GAF: 36 months)	1 SR (1 RCT; N=170)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 0.40 (-2.47 to 3.27)	Low
Function: Global Function (Non-Integrated: mean RFS score; 6 months)	1 SR (1 RCT; N=50)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD -0.78 (-2.91 to 1.35)	Insufficient
Function: Global Function (Non-Integrated: mean RFS score; 6 months)	1 SR (1 RCT; N=29)	Moderate	Unknown	Direct	Imprecise	MD -2.67 (-5.28 to -0.06)	Insufficient

Outcome	Number of studies Number of subjects	Study limitations	Consistency	Directness	Precision	Magnitude of effect: Summary effect size (95% CI)	Strength of evidence (high, moderate, low, insufficient)
Ability to maintain treatment (6 months)	1 SR (3 RCTs; N=134)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.23 (0.73 to 2.06)	Insufficient
Ability to maintain treatment (18 months)	1 SR (3 RCTs; N=134)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.35 (0.83 to 2.19)	Insufficient

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