VA/DoD Clinical Practice Guidelines

VA/DoD Clinical Practice Guideline for the Management of First-Episode Psychosis and Schizophrenia

Provider Summary

Version 1.0 | 2023

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF FIRST-EPISODE PSYCHOSIS AND SCHIZOPHRENIA

Department of Veterans Affairs

Department of Defense

Provider Summary

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DoD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

Version 1.0 – April 2023

Table of Contents

Introduction

The VA and DoD Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the VA/DoD Health Executive Committee "on the use of clinical and epidemiological evidence to improve the health of the population . . ." across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPG) for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and wellbeing.

The VA/DoD EBPWG initiated the creation of the VA/DoD First-Episode Psychosis and Schizophrenia CPG in 2021. This CPG provides an evidence-based framework for evaluating and managing care for patients with schizophrenia toward improving clinical outcomes. Successful implementation of this CPG will

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care;
- Emphasize the use of patient-centered care and shared decision making;
- Minimize preventable complications and morbidity; and
- Optimize individual health outcomes and quality of life (QoL).

The full VA/DoD Schizophrenia CPG, as well as additional toolkit materials including a Quick Reference Guide and Patient Summary, can be found at: https://www.healthquality.va.gov/index.asp.

Recommendations

The evidence-based clinical practice recommendations listed (see Table 1) were made using a systematic approach considering four domains as per the GRADE approach (see Methods and Appendix A in the full text Schizophrenia CPG). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 1. Evidence-based Clinical Practice Recommendations with Strength and Category

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Assessment and Evaluation	*Suspected Psychosis*	1.	For individuals with suspected psychosis, we suggest using evidence-based screening tools in specialty mental health settings to differentiate/identify individuals at risk for transition to psychosis.	Weak for	Reviewed, New-added
		2.	For individuals with suspected psychosis, there is insufficient evidence to recommend for or against biomarker screening tools (e.g., magnetic resonance imaging–based prediction system, serum biomarker panels) to differentiate/identify individuals at risk for transition to psychosis.	Neither for nor against	Reviewed, New-added
Management of First-Episode Psychosis and Schizophrenia	*First-Episode Psychosis*	3.	We recommend treatment/management with early intervention services for individuals with first-episode psychosis.	Strong for	Reviewed, New-added
		4.	We recommend the use of family interventions (including problem solving–based self-learning, education, and mutual family support) for individuals with first-episode psychosis.	Strong for	Reviewed, New-added
		5.	We suggest the use of the Individual Placement and Support model of supported employment for individuals with first-episode psychosis with a goal of employment and/or education.	Weak for	Reviewed, New-added
		6.	There is insufficient evidence to recommend for or against any specific duration for participation in specialized early intervention services for individuals with first-episode psychosis.	Neither for nor against	Reviewed, New-added
		7.	There is insufficient evidence to recommend for or against a specific duration for treatment with antipsychotic medication after response or remission for individuals with first-episode psychosis.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (continued)	*Pharmacologic Interventions for Psychosis*	8.	We recommend the use of an antipsychotic medication other than clozapine for the treatment of an acute episode in individuals with schizophrenia or first-episode psychosis who have previously responded to antipsychotic medications. The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.	Strong for	Reviewed, New-added
		9.	We recommend the use of an antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization in individuals with schizophrenia who have responded to treatment. Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications.	Strong for	Reviewed, New-added
		10.	We suggest a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication. Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications.	Weak for	Reviewed, New-added
		11.	We suggest offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia.	Weak for	Reviewed, New-added
		12.	We recommend the use of clozapine for individuals with treatment-resistant schizophrenia.	Strong for	Reviewed, New-added
		13.	We suggest augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine.	Weak for	Reviewed, New-added
	Pharmacologic Interventions for Treatment of Side Effects	14.	There is insufficient evidence to recommend for or against any treatment for hyperprolactinemia-related side effects of antipsychotic medications in individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		15.	We suggest using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia.	Weak for	Reviewed, New-added
		16.	We suggest a trial of a vesicular monoamine transporter 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia.	Weak for	Reviewed, New-added
		17.	We suggest a trial of diphenhydramine for individuals with schizophrenia who are experiencing sialorrhea as a side effect of clozapine.	Weak for	Reviewed, New-added
		18.	There is insufficient evidence to recommend for or against augmentation with any non-antipsychotic medication for treatment of cognitive and/or negative symptoms for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (continued)	***Non-pharmacologic Interventions***	19.	We recommend the use of psychosocial interventions provided to a primary support person or family member to decrease the risk of relapse and hospitalization for individuals with schizophrenia.	Strong for	Reviewed, New-added
		20.	We recommend the use of service models based on standard Assertive Community Treatment in individuals with schizophrenia evidencing severe functional impairments and/or risk for repeated hospitalizations.	Strong for	Reviewed, New-added
		21.	We recommend the use of the Individual Placement and Support model of supported employment for individuals with schizophrenia with a goal of employment.	Strong for	Reviewed, New-added
		22.	There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with schizophrenia experiencing housing insecurity.	Neither for nor against	Reviewed, New-added
		23.	We suggest compensatory cognitive training programs for the treatment of cognitive impairment for individuals with schizophrenia.	Weak for	Reviewed, New-added
		24.	We suggest offering skills training for individuals with schizophrenia evidencing severe and persistent functional impairments and/or deficits in social, social-cognitive, and problem-solving skills.	Weak for	Reviewed, New-added
		25.	There is insufficient evidence to recommend for or against transcranial direct current stimulation and repetitive transcranial magnetic stimulation for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		26.	There is insufficient evidence to recommend for or against electroconvulsive therapy for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		27.	There is insufficient evidence to recommend for or against the use of motivational interviewing or shared decision making to improve medication adherence for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		28.	There is insufficient evidence to recommend for or against the use of the Clubhouse model for vocational rehabilitation to increase employment outcomes for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		29.	There is insufficient evidence to recommend for or against the use of targeted peer-provided interventions for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		30.	We suggest adding aerobic exercise to treatment as usual to reduce symptoms and improve functioning for individuals with schizophrenia.	Weak for	Reviewed, New-added
		31.	We suggest offering yoga as an adjunct to other evidence-based treatments for positive and negative symptoms for individuals with schizophrenia.	Weak for	Reviewed, New-added
		32.	We suggest cognitive behavioral therapy for psychosis in combination with pharmacotherapy for individuals with prodromal and early psychosis.	Weak for	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (continued)	*Non-pharmacologic Interventions (continued)*	33.	We suggest the following psychotherapies and psychotherapeutic interventions in combination with pharmacotherapy for individuals with schizophrenia: • Cognitive behavioral therapy or cognitive behavioral therapy for psychosis, • Acceptance and mindfulness-based therapies, • Metacognitive therapy, or • Positive psychology interventions.	Weak for	Reviewed, New-added
		34.	There is insufficient evidence to recommend for or against Illness Management and Recovery in combination with pharmacotherapy for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		35.	There is insufficient evidence to recommend for or against virtual reality interventions, including avatar therapy, for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		36.	We suggest using telephone-based care management to reduce rehospitalization days for individuals with schizophrenia.	Weak for	Reviewed, New-added
		37.	There is insufficient evidence to recommend for or against augmenting pharmacotherapy with acupuncture to reduce negative and positive symptoms for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		38.	There is insufficient evidence to suggest case management to improve preventive screening and/or medical outcomes for individuals with schizophrenia.	Neither for nor against	Reviewed, New-added
		39.	We recommend a face-to-face individualized smoking cessation intervention tailored specifically to the patient for individuals with schizophrenia.	Strong for	Reviewed, New-added
Management of Co-occurring Conditions		40.	We suggest the use of dietary interventions, exercise, individual lifestyle counseling, and/or psychoeducation for metabolic side effects of antipsychotic medication as well as the delivery of weight management services that are based on a chronic care model (e.g., Enhancing Quality of Care in Psychosis) for individuals with schizophrenia.	Weak for	Reviewed, New-added
		41.	There is insufficient evidence to recommend specific, integrated, non-integrated, or psychosocial treatments in addition to usual care for individuals with schizophrenia and comorbid substance use disorder.	Neither for nor against	Reviewed, New-added

[a] Additional information is available in the full CPG: see Determining Recommendation Strength and Direction.

[b] Additional information is available in the full CPG: see Recommendation Categorization.

Scope of the CPG

This CPG is based on published clinical evidence and related information available through November 31, 2021. It is intended to provide general guidance on best evidence-based practices (see Appendix A in the full CPG for additional information on the evidence review methodology). Although the CPG is intended to improve the quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

The patient population of interest for this CPG is adults with schizophrenia, schizophrenia spectrum disorders, schizoaffective disorder, schizophreniform disorder, or FEP being treated in any setting. It includes Veterans and Service members eligible for care in the VA or DoD health care delivery systems as well as those who receive care from community-based providers and their dependents. Recommended interventions in this CPG are applicable regardless of care setting, unless otherwise indicated, for any individual in the VA and DoD health care systems.

This CPG is intended for use by VA and DoD providers to care for patients with schizophrenia, including primary care providers (PCP), mental health providers, and others involved in the health care team. Additionally, this CPG is intended for community-based providers involved in the care of active duty Service members, beneficiaries, or Veterans with schizophrenia.

Guideline Development Team

Table 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Ira Katz, MD, PhD (Champion)**
	Sandra Resnick, PhD (Champion)
	Kim Bronson, NP
	Robert Buchanan, MD
	Ann Canastra, MS, NCC, LMHC, ACS, MSW, LPC
	Matthew A. Fuller, PharmD, FASHP, BCPP
	Richard Goldberg, PhD
	Marcia Hunt, PhD
	Noosha Niv, PhD
	Koren Purvis, MD

Organization	Names*
Department of Defense	**LTC Shannon C. Ford, MD, FAPA (Champion)**
	Fuad Issa, MD, FAPA (Champion)
	LTC Marlene Arias-Reynoso, DNP, PMHNP-BC
	Jennifer L. Bell, MD
	Lt Col Pamela Blueford, LICSW
	MAJ Lola Buchanan, RN, PMHN-BC, MHA, BSN
	Rachel Coller, PharmD
	Pia Khandekar, PsyD
	Kate McGraw, PhD
	Jared J Solomon, MD
	Raquel Williams, MD
VA Evidence Based Practice, Office of Quality and Patient Safety ***Veterans Health Administration***	James Sall, PhD, FNP-BC
	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
	René Sutton, BS, HCA
	Eric Rodgers, PhD, FNP-BC
Clinical Quality Improvement Program ***Defense Health Agency***	Elaine Stuffel, MHA, BSN, RN
	Lisa Jones, BSN, RN, MHA, CPHQ
	Cynthia Villarreal, BSN, RN
The Lewin Group	Clifford Goodman, PhD
	Jennifer Weil, PhD
	Erika Beam, MS
	Charlie Zachariades, MSc
	Peter Baroff, BA
	Annie Zhang, BA
	Andrea Dressel, BS
ECRI	James Reston, PhD, MPH
	Stacey Uhl, PhD
	Allison Hedden-Gross, MS, MLS
Sigma Health Consulting	Frances M. Murphy, MD, MPH
	James Smirniotopoulos, MD
Duty First Consulting	Anita Ramanathan, BA
	Mary Kate Curley, BA
	Kate Johnson, BA
	Rachel Piccolino, BA
	Richa Ruwala, BA

* Additional contributor contact information is available in Appendix H (in the full VA/DoD Schizophrenia CPG).

Patient-centered Care

Intended to consider patient needs and preferences, guideline recommendations represent a whole/holistic health approach to care that is patient centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and wellbeing.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(60, 61) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and wellbeing goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnicity, and other differences.

Shared Decision Making

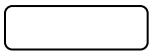
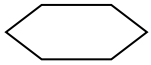
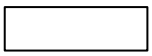
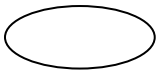
This CPG encourages providers to practice shared decision making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(62) Shared decision making is emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM), now NAM, report in 2001 (63) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care or both, especially where patient heterogeneity in weighing risks and benefits might exist. Veterans Health Administration and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in managing patients with FEP or schizophrenia. This algorithm format represents a simplified flow of the management of patients with schizophrenia and helps foster efficient decision making by providers. It includes

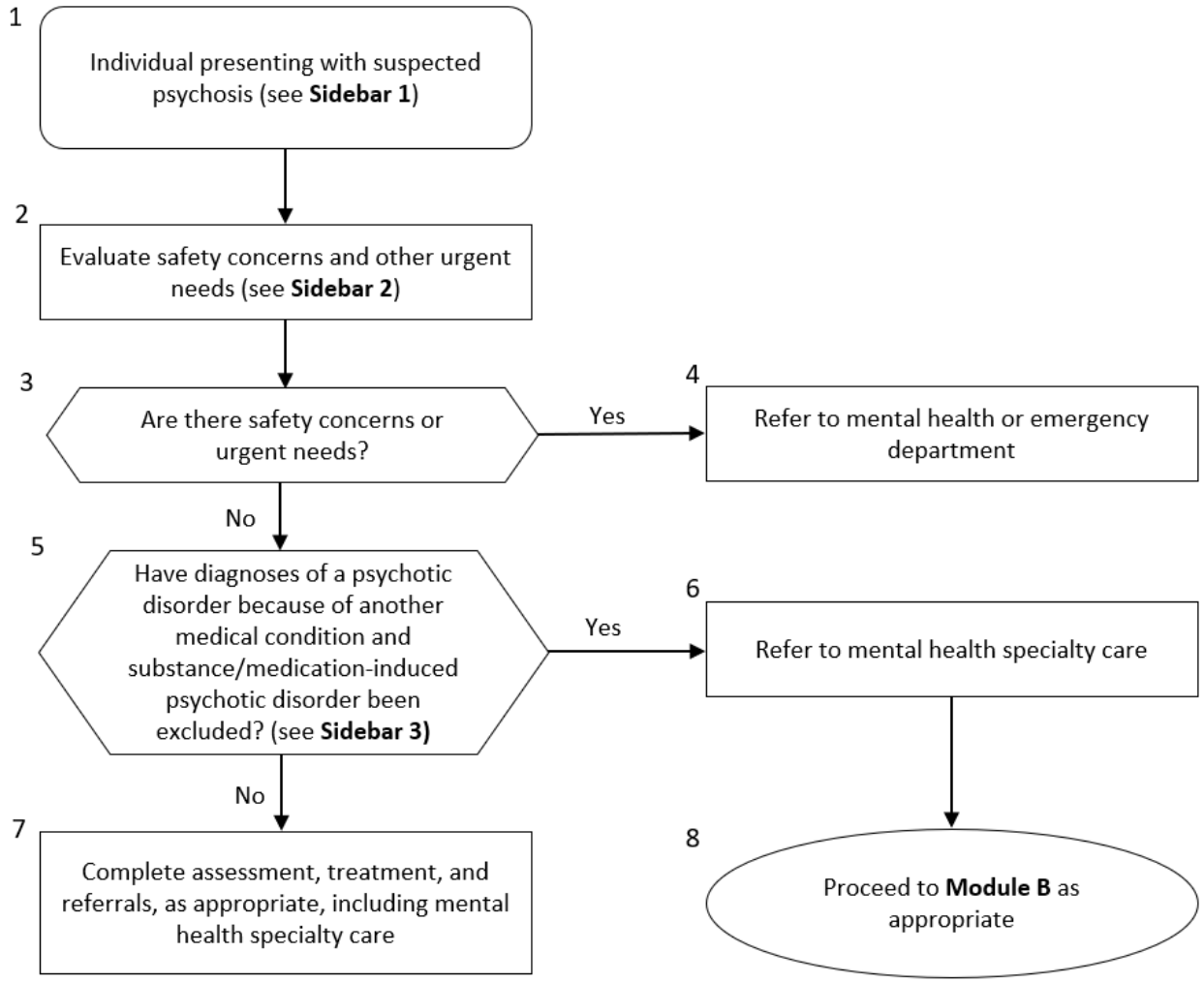
- Steps of care in an ordered sequence,
- Decisions to be considered,
- Decision criteria recommended, and
- Actions to be taken.

The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(6) Sidebars 1–7 provide more detailed information to assist in defining and interpreting elements in the boxes.

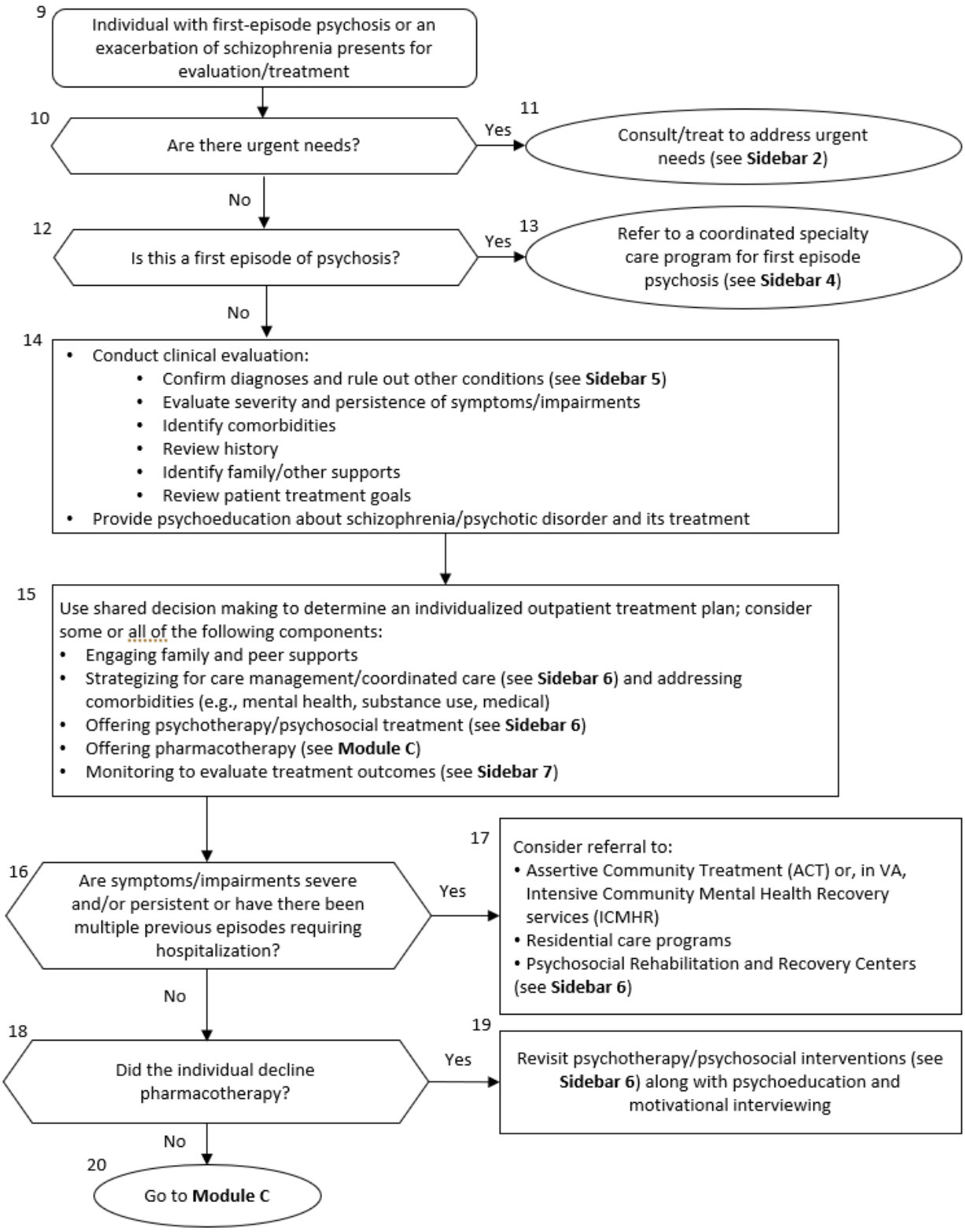
Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered "Yes" or "No."
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the algorithm.

Appendix J in the full Schizophrenia CPG contains alternative text descriptions of the algorithms.

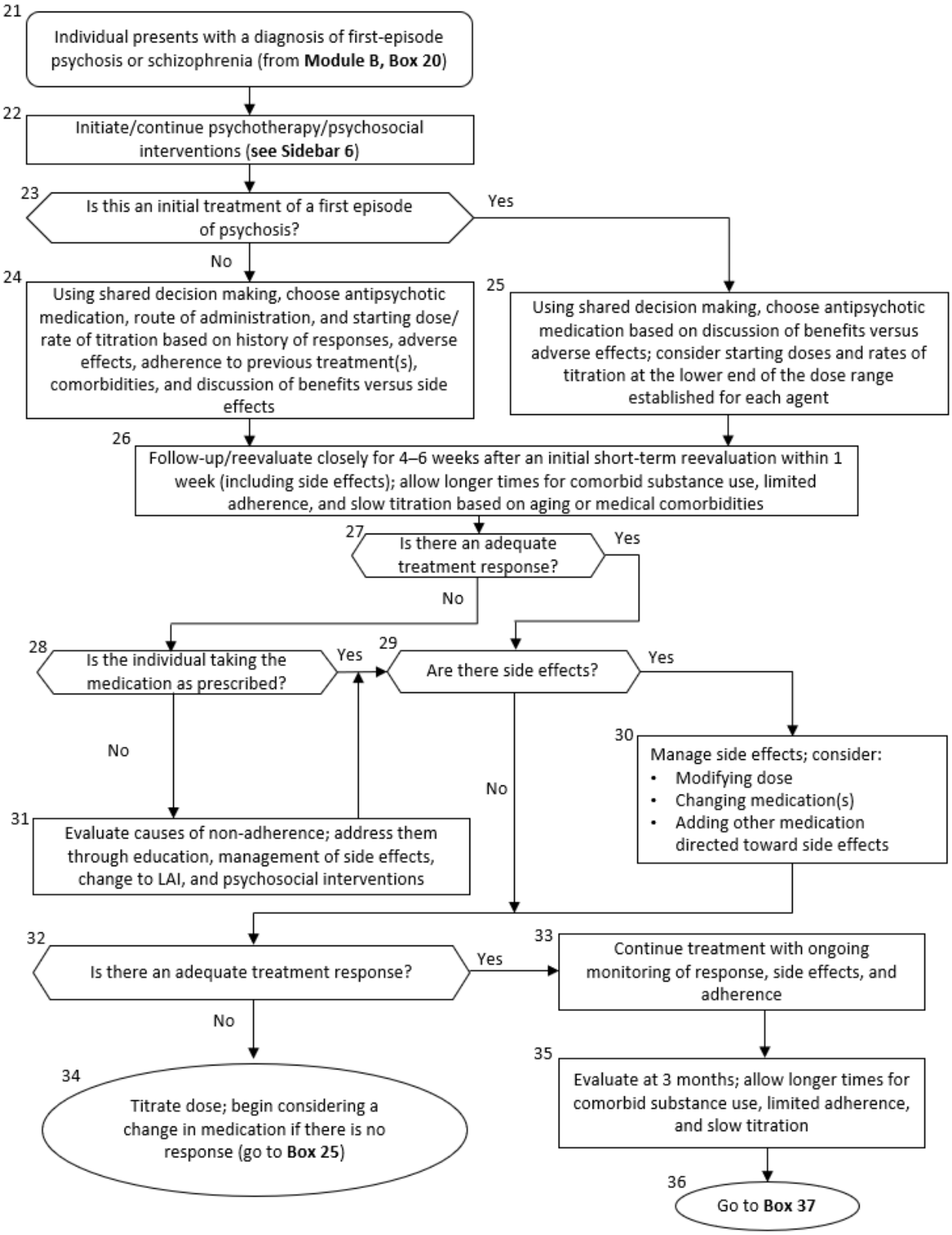
Module A: Primary Care Evaluation and Management of Suspected Psychosis or Possible Schizophrenia

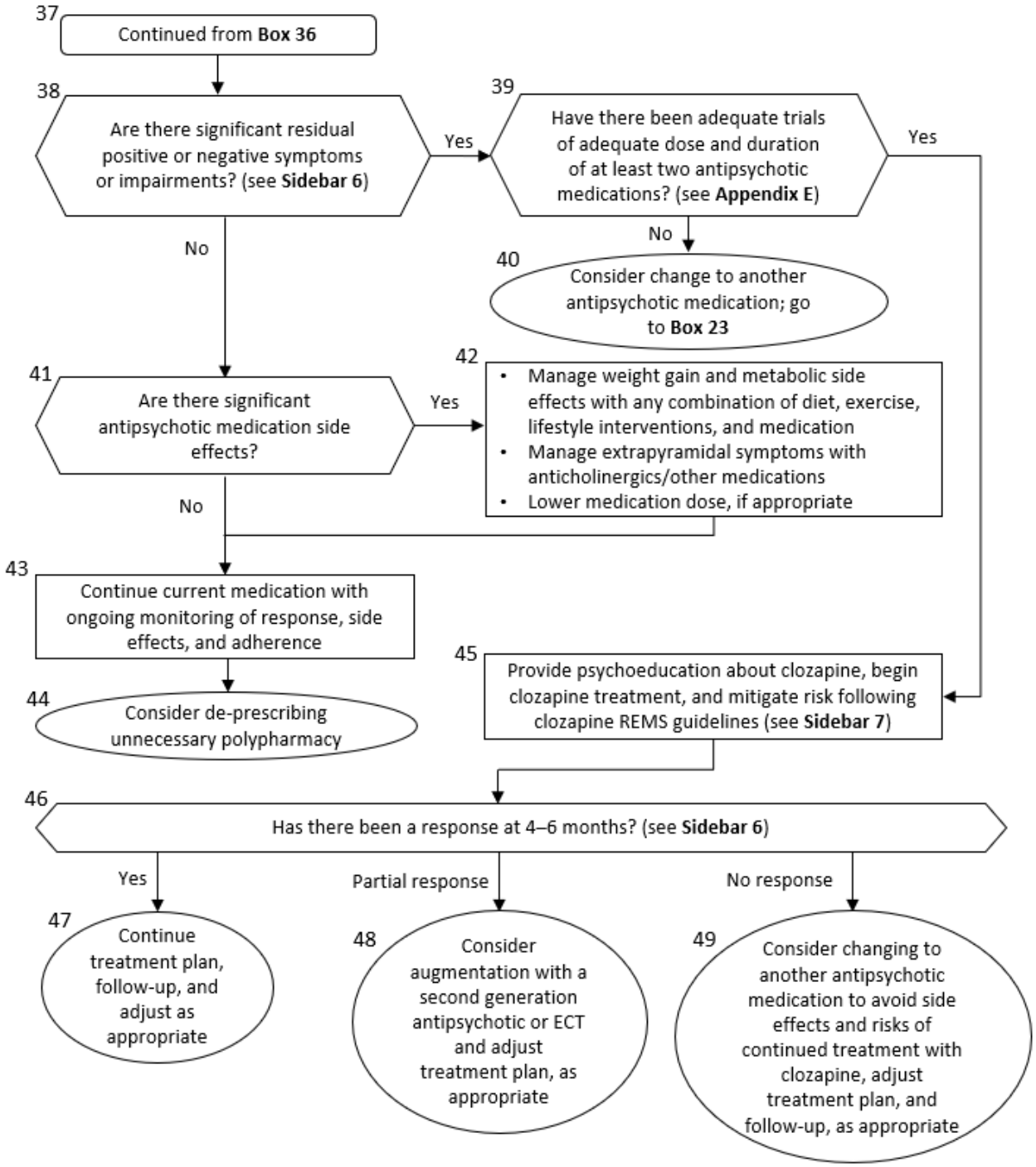


Module B: Evaluation and Management of First-Episode Psychosis and Schizophrenia by Mental Health Providers



Module C: Pharmacotherapy for Treatment of First-Episode Psychosis and Schizophrenia





Abbreviations: ECT: electroconvulsive therapy; REMS: Risk Evaluation and Mitigation

Sidebar 1: Early Warning Signs of Psychosis (7)

Changes that suggest possible delusions, hallucinations, disorganization, functional impairments, unexplained deteriorations in performance, cognition, or both

- Worrisome drop in grades or job performance
- New trouble thinking clearly or concentrating
- Suspiciousness, paranoid ideas, or uneasiness with others
- Social withdrawal or more time spent alone than usual
- Unusual, overly intense new ideas, strange feelings, or no feelings at all
- Decline in self-care or personal hygiene
- Difficulty telling reality from fantasy
- Confused speech or trouble communicating

Sidebar 2: Indications for Urgent Specialty Care Consultation

- Serious homicidal ideation or aggressive or violent behaviors or both
- Serious suicidal ideation (e.g., suicidal ideation with plan or intent, history of suicide-related behavior)
- Self-harm or behavior that might be preparatory for suicide
- Command hallucinations that might impair safety (e.g., commands to harm oneself or others or to engage in dangerous activities)
- Catatonia or grossly disorganized speech or behaviors
- Serious self-neglect or apparent inability to meet basic needs

Signs of delirium, including an altered level of consciousness, require a comprehensive evaluation (including toxicology and drug screens and consideration of medical illness, infection, or injury) performed before behavioral health referral.

Sidebar 3: Medical Conditions, Medications, Toxins, and Substances That Can Cause Psychoses (7)

Medical conditions

- Neurological conditions (e.g., neoplasm, cerebrovascular disease, Huntington's disease, Parkinson's disease, multiple sclerosis, epilepsy, auditory or visual nerve injury or impairment, deafness, migraine, central nervous system infection)
- Endocrine conditions (e.g., hyper- and hypothyroidism, hyper- and hypoparathyroidism, hyper- and hypoadrenocorticism)
- Metabolic conditions (e.g., hypoxia, hypercarbia, hypoglycemia, vitamin B12 deficiency, fluid or electrolyte imbalances, hepatic or renal diseases)
- Autoimmune disorders with central nervous system involvement (e.g., systemic lupus erythematosus, N-methyl-d-aspartate [NMDA] receptor autoimmune encephalitis)

Medications, toxins, and substances of abuse

- Specific classes of medications (i.e., anesthetics and analgesics, anticholinergic agents, anticonvulsants, antihistamines, antihypertensive and cardiovascular medications, antimicrobial medications, antiparkinsonian medications, chemotherapeutic agents [e.g., cyclosporine, procarbazine], corticosteroids, gastrointestinal medications, muscle relaxants, nonsteroidal anti-inflammatory medications, other over-the-counter medications [e.g., phenylephrine, pseudoephedrine], antidepressant medications, and disulfiram)
- Specific classes of toxins (i.e., anticholinesterase, organophosphate insecticides, sarin and other nerve gases, carbon monoxide, carbon dioxide, and volatile substances such as fuel or paint)
- Intoxication with substances of abuse (i.e., alcohol; cannabis; hallucinogens, including phencyclidine and related substances; inhalants; sedatives, hypnotics, and anxiolytics; stimulants, including cocaine)
- Withdrawal from substances of abuse (i.e., alcohol; sedatives, hypnotics, and anxiolytics)

Sidebar 4: Coordinated Specialty Care (8)

Early intervention services for individuals experiencing FEP include coordination of the evidence-based treatments described below.

- **Team-Based Care** – All CSC providers are trained in the principles of team-based care for youth and young adults with FEP and participate in weekly team meetings to improve coordination and quality of care. Team members receive ongoing supervision, consultation, or both to maintain fidelity to the CSC model.
- **Recovery-Oriented Psychotherapy** – Individual psychotherapy for FEP is based on cognitive-behavioral treatment principles. It emphasizes resilience training, illness and wellness management, and general coping skills pertinent to young adults experiencing a first psychotic episode. Psychological interventions are essential for symptomatic and functional recovery and might aid in the prevention of comorbidities, such as SUDs.
- **Family Psychoeducation and Support** – FEP can devastate the individual's relatives and other support persons, who struggle to adjust to changed circumstances and new demands. Family psychoeducation and support teaches family members or other individuals providing support about psychosis and its treatment and strengthens their capacity to aid in the individual's recovery.
- **Supported Employment Services** – For young adults, FEP can impede attempts to obtain or maintain employment. Supported employment services are offered to all clients who want to work to help them choose and get a job that aligns with their career goals. Supported employment emphasizes rapid job placement in the client's preferred work setting. Ongoing supports are also available to help the individual maintain employment.
- **Supported Education Services** – The experience of FEP can disrupt school attendance and academic performance. Supported education services facilitate an individual's return to school as well as the attainment of expected educational milestones. Supported education emphasizes rapid placement in the individual's desired school setting and provides active coaching and support to ensure the individual's educational academic success.
- **Pharmacotherapy and Primary Care Coordination** – Guideline-based use of medication optimizes the speed and degree of symptomatic recovery by individuals with FEP and minimizes the likelihood of side effects. Pharmacotherapy is best initiated following a thorough medical evaluation to assess for all possible causes of psychosis. Pharmacotherapy typically begins with a low dose of a single antipsychotic medication and involves monitoring for symptom response, side effects, and attitudes toward medication at every visit. Consideration of use of a long-acting injectable as part of a holistic approach is common practice.
  - CSC places special emphasis on monitoring and managing cardiometabolic risk factors, such as smoking, weight gain, hypertension, dyslipidemia, and pre-diabetes. Prescribers maintain close contact with primary care providers to ensure optimal medical treatment for risk factors related to cardiovascular disease and diabetes.
- **Case Management** – Case management assists clients with solving practical problems and coordinates services across multiple areas of need. Case management involves frequent in-person contact between the provider and the individual and family members, with sessions occurring in clinic, community, and home settings, as required.

Abbreviations: CSC: coordinated specialty care; FEP: first-episode psychosis; SUD: substance use disorder

Sidebar 5: Psychosocial Interventions and Supportive Services

All individuals with schizophrenia should have access to a range of psychosocial interventions and supportive services fully integrated into their care. Individuals should make decisions about participation in interventions as part of a treatment planning process using shared decision making in which interventions are linked to the individual's identified needs, preferences, and life goals. Psychosocial interventions include, but are not limited to, the following.

- CBT, CBT for psychosis (CBTp), or both (If the individual has had a prior course of CBT or CBTp, consider booster sessions or another psychotherapy, such as acceptance- or mindfulness-based therapies, positive psychotherapies, or meta-cognitive therapy.)
- Skills training for impairments in social skills
- Cognitive training, cognitive remediation, or both for cognitive deficits
- Supported employment for individuals with a goal of employment
- Supported education for individuals with educational goals
- Illness self-management approaches (e.g., illness management and recovery)
- Evidence-based psychotherapies for comorbid disorders
- Caregiver-directed psychosocial interventions for family, others with whom the individual with schizophrenia maintains close contact and chooses as family, or both
- Peer support and peer support groups (e.g., Vet-to-Vet)
- Interventions to assist individuals with coping with stigma, addressing self-stigma, and issues of disclosure

Supportive services should be available to assist with additional sequelae to living with psychiatric disability and offered as needed.

- Consider Housing First, other supported housing models, or both for individuals with housing instability or who are unhoused.
- Offer case management, other supportive services, or both to assist with unstable housing or lack of access to food, clothing, and other basic needs.
- Offer benefits counseling and support for financial management (e.g., assistance with banking, budgeting).
- Provide informal caregiver support, as needed.
- Offer parenting assistance.
- Provide legal support, including assisting in transitions with the legal system.
- Coordinate reevaluations of psychotherapy and rehabilitation- or recovery-oriented treatments with reevaluations of pharmacotherapy.
- Consider increasing the intensity of psychosocial treatments to address increased needs when responses to medication have been inadequate and in response to increased opportunities when pharmacologic treatment leads to decreases in impairments.

Abbreviation: CBT: cognitive behavioral therapy

Sidebar 6: Monitoring Response to Intervention

Consider the following monitoring parameters.

- Reduction core symptoms of psychosis, schizophrenia, or both
- Lab parameters (per REMS requirements, QTc, or both; leukocytes; neutrophils; agranulocytes; sodium; glucose; hemoglobin A1C; triglycerides; high-density and low-density cholesterol; prolactin, if risperidone or paliperidone is used; prolactin, if unexpected breast tissue changes occur; CPK in the case of new-onset movement disorder and as appropriate through the course of movement disorders) – measure at baseline, three months (for clozapine and olanzapine) and at least annually thereafter if treated with antipsychotic medications
- Extrapyramidal movements (cogwheel rigidity, akathisia, parkinsonism, TD, acute and painful muscle tone changes)
- Vitals (weight, temperature, blood pressure, HR changes, orthostatic hypotension, autonomic instability, unexplained fever)
- Functioning (social functioning, intimacy, sexuality, parenting, workplace, education, family or other primary support group, interpersonal baseline changes)
- Durable planning needs (financial; guardianship; medical, legal, or both; will)
- Patient goals and preferences
- Life circumstances changes

Notes: Monitoring response timeframe varies during an acute episode, stabilization period or both, versus during a recovery period or period of chronic symptomatic stability. Monitoring of vitals, mental status functioning, and movement status are recommended at every follow-up as part of common everyday practice standards. The timing and length between follow-up appointments naturally vary with current status and circumstance. Phase of life, reproductive or sexuality status or both, relative youth, comorbidity, and advanced age considerations are frequently overlooked yet have large quality impacts on individuals when assessed and holistically addressed. Patients in an inpatient status should be monitored daily in accordance with an established hospital treatment plan. Life circumstance, life functioning, and durable planning needs should be reassessed at a minimum during times of significant of major status change (e.g., as part of a hospital discharge process; at times of community capability changes; at the request of the patient, the significantly involved members of the care and support structures, or both; or the legal system).

Abbreviations: CPK: creatine phosphokinase; REMS: Risk Evaluation and Mitigation Strategy; QTc: QT corrected QT-interval; A1C: glycated hemoglobin; HR: heart rate; TD: tardive dyskinesia

Sidebar 7: Clozapine Management

1. Provide the patient (and, where appropriate, the family) education about the benefits and risks of clozapine, and ensure their understanding and consent.
2. Ensure that the prescriber and the pharmacy are registered with Clozapine REMS.
3. Confirm indications for clozapine: treatment-resistant schizophrenia; schizophrenia or schizoaffective disorder with suicidality; or, possibly, schizophrenia with persistent aggressive behavior.
4. Evaluate symptoms and impairments with standardized assessment instruments.
5. Consider whether the patient might have BEN as defined by Clozapine REMS.
6. Register the patient with Clozapine REMS (see note).
7. Obtain and provide Clozapine REMS with a within-range absolute neutrophil count before prescribing and dispensing (see note).
8. Prescribe clozapine starting at low doses with gradual titration to therapeutic doses and blood levels.
9. Monitor absolute neutrophil counts weekly for six months, then once every two weeks for six months, then monthly, thereafter; report results to Clozapine REMS (see note).
10. Follow Clozapine REMS protocols for below-threshold absolute neutrophil counts indicating neutropenia or agranulocytosis.
11. Obtain troponin and c-reactive protein levels at baseline and monitor them weekly for at least the first month of treatment to support the early identification of myocarditis as an adverse effect.
12. Consider prescribing bowel regimens to prevent clozapine-related gastrointestinal hypomotility and ileus, especially when the patient is also receiving other anticholinergic medications.
13. Monitor symptoms, impairments, and side effects.
14. Evaluate blood levels and adjust doses as appropriate to evaluate non-response, possible non-adherence, pharmacokinetic drug-drug or drug-smoking interactions and to support management of side effects.

Note: In VA, the National Clozapine Coordinating Center (NCCC) serves as an intermediary between prescriber and Clozapine REMS for registration of patients starting clozapine and reporting of absolute neutrophil levels. For additional information, see https://www.newclozapinerems.com/home#.

Abbreviations: BEN: benign ethnic neutropenia; REMS: Risk Evaluation and Mitigation Strategy

Additional Educational Materials and Resources

For additional information on schizophrenia, several topic-specific resources published by VA and SAMHSA pertain to the content described in this CPG. These resources, (see Table 3) might offer additional information about numerous topics in the care and management of patients with schizophrenia. The Work Group has not reviewed the scientific content or quality of any of those materials and is not in a position to endorse them.

Table 3. Schizophrenia/Serious Mental Illness Education Resources

Resource		Description	Website
Provider Education Resources	SMI Adviser	Clinical support system for SMI sponsored by American Psychiatric Association and SAMHSA	https://smiadviser.org/
	VA VISN 2 MIRECC	Mission to maximize recovery using translational research methods for Veterans with SMI or suicidal ideation and behavior	https://www.mirecc.va.gov/visn2/
	VA VISN 5 MIRECC	Mission to maximize recovery and community functioning of Veterans with SMI	https://www.mirecc.va.gov/visn5/
	VA VISN 22 MIRECC	Mission to improve long-term functional outcome of Veterans with psychotic mental disorders	https://www.mirecc.va.gov/visn22/
Consumer Education Resources	NIMH	Lead federal agency on research in mental health disorders	https://www.nimh.nih.gov/health/topics/schizophrenia https://www.nimh.nih.gov/health/publications/schizophrenia-listing
	SMI Adviser	Clinical support system for SMI sponsored by APA and SAMHSA	https://smiadviser.org/
	VA Office of Mental Health and Suicide Prevention	Schizophrenia education and VA services	https://www.mentalhealth.va.gov/schizophrenia/index.asp
Support	NAMI	Provider of advocacy, education, support, and public awareness so all individuals and families affected by SMI can build better lives	https://www.nami.org/home
	National Suicide Prevention Lifeline	Free, confidential resource for individuals in crisis	https://www.veteranscrisisline.net/

Resource		Description	Website
Treatment Locators	Get Help from a TRICARE Provider or Treatment Facility	TRICARE Treatment Locator	https://tricare.mil/
	Get Help at VA	VA Treatment Locator	https://www.va.gov/find-locations/
	Get Help in the Community	SAMHSA Behavioral Health Treatment Services Locator	https://findtreatment.samhsa.gov/
	Get Help for Recent Onset SMI	SAMHSA Early SMI Treatment Locator	https://www.samhsa.gov/esmi-treatment-locator
	Get Help for At-Risk/Early Psychosis	PEPPNET: national network of programs providing services to individuals at risk for or experiencing early psychosis	https://med.stanford.edu/peppnet.html
	inTransition	Provider of individualized coaching support to Service members and Veterans transitioning between mental health or behavioral health care providers and health care systems. Patient participation in inTransition is 100% voluntary, and a patient may withdraw from the program at any time.	https://www.health.mil/Military-Health-Topics/Centers-of-Excellence/Psychological-Health-Center-of-Excellence/inTransition
Other	VA Moving Forward	Training course that helps with common challenges, such as stress management, relationship difficulties, coping with physical injury, financial difficulties, and adjustment issues	https://www.veterantraining.va.gov/movingforward/
	Personal Story of Mental Illness	Video Story of Mental Illness in Difficult Times (An Asian American's Story)	https://youtu.be/usI6PDwMjcw

Abbreviations: APA: American Psychiatric Association; MIRECC: Mental Illness Research, Education, and Clinical Center; NAMI: National Alliance on Mental Illness; NIMH: National Institute of Mental Health; PEPPNET: Psychosis-Risk and Early Psychosis Program Network; SAMHSA: Substance Abuse and Mental Health Services Administration; VA: Department of Veterans Affairs; VINS: Veterans Integrated Services Network

Strategies That Promote Engagement of Family and Other Support

Rationale for Including Family Members in Treatment. Mental illness affects the whole family. "Family" is defined broadly as family members, significant others, caretakers, and other supportive people (e.g., friends, roommates). Family services teach families to work together toward recovery. Families attend educational sessions where they learn basic facts about mental illness, coping skills, communication skills, problem-solving skills, and ways to work with one another toward recovery. Patients who participate in family interventions experience fewer psychiatric symptoms and relapses, improved treatment adherence, and improved family functioning. Family members also benefit and report feeling more satisfaction with their relationship and less burden.

When to Consider Involving Family Members. Providers should consider involving family members in care for any Veteran who relapses frequently, is at risk for relapse, experiences persistently exacerbated symptoms, or is in a transitional point in life and needs social support. Family involvement should also be considered for any family member who needs education or support or makes frequent contact with treatment teams because of concerns about the Veteran. Contraindications to family involvement might include Veterans' preference not to include family, abuse, trauma, divorce, custody, inheritance, and financial support. Individual circumstances surrounding sensitive clinical and legal issues should be carefully explored to avoid potential damage to, or exploitation of, the Veteran.

Range of Family Services. There is a range of family programs available to fit the specific needs of each family. Some families benefit from just a few sessions, although more intensive services are especially helpful for families experiencing high levels of stress and tension and for people who are chronically symptomatic or prone to relapse. Providers are encouraged to consider a continuum of care in deciding how family members can be integrated in treatment.

Engaging family members in care begins with the Veteran. Motivational Interviewing techniques can be used to engage Veterans in family services by exploring the role they want their family to play in their recovery and their preferences about family participation. This engagement handout was designed to engage Veterans in Behavioral Family Therapy, but it can be used to engage Veterans in any type of family service. More information is available at https://www.mirecc.va.gov/visn22/familyconsultation_veteran_engagement.pdf.

Veteran-Centered Brief Family Consultation. Veteran-Centered Brief Family Consultation (VCBFC) is a brief intervention designed to integrate family, chosen supports, or both into their Veteran's recovery process. The intervention is typically 1–3 sessions with a maximum of five sessions. Family Consultation can also be used as a first step in assessment or treatment planning when considering more intensive family therapies, such as Behavioral Family Therapy. Visit

https://www.mirecc.va.gov/visn22/Veteran_Centered_Brief_Family_Consultation.asp for resources to implement VCBFC into clinical practice, including assessment, education, skills training, and other intervention handouts.

Training in VCBFC is available on TMS (Course #37314) and is approved for four continuing education units (CEU) for most licensed mental health professionals. Individuals who do not need CEUs can request an instructional DVD or CD set at https://www.mirecc.va.gov/visn22/Veteran_Centered_Family_Consultation_DVD.asp.

Behavioral Family Therapy (BFT) is for families with more significant needs. Sessions focus on family education, communication skills training, and problem-solving skills training. BFT generally lasts 6–9 months and can be conducted in single-family or multi-family formats. An instructional DVD/CD set is available at https://www.mirecc.va.gov/visn22/Behavioral_Family_Therapy_DVD.asp.

Coaching into Care is a free service for families and friends of Veterans. Responders will briefly assess concerns and provide appropriate resources and referrals. Through 10- to 30-minute calls, licensed psychologists and social workers offer guidance and help for starting conversations with a Veteran about their mental health or substance use and motivating them to seek treatment if it is needed. Family and friends can call (888) 823-7458. More information is available at https://www.mirecc.va.gov/coaching/.

NAMI Family-to-Family is a free, 8-session educational program for family members, significant others, and friends of people with mental health conditions. Sessions are led by a NAMI-trained family member and include presentations, discussions, and exercises pertinent to managing a psychiatric illness successfully. More information is available at https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Family-to-Family.

NAMI Homefront is a free, 6-session educational program for families, caregivers, and friends of military service members and veterans with mental health conditions. It is based on the NAMI Family-to-Family program but is designed to address the unique needs of family, caregivers, and friends of those who have served or are currently serving. More information is available at https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Homefront.

Support and Family Education Model (SAFE) is a 10-session family education program for people who care about someone living with mental illness or PTSD. The treatment manual and implementation tools are available at: https://www.ouhsc.edu/safeprogram/.

SAMHSA Family Psychoeducation Evidence-Based Practices Toolkit offers evidence-based practices to help public officials develop family psychoeducation mental health programs. The kit can be found at: https://store.samhsa.gov/product/Family-Psychoeducation-Evidence-Based-Practices-EBP-KIT/SMA09-4422

Pharmacotherapy

Table 4: Antipsychotic Oral Dosing and Dosage Forms – First-Generation Antipsychotics [a,b,c,d,e,f,g]

Medication	Dosage Form or Forms	Initial Oral Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Chlorpromazine	T: 10mg, 25 mg, 50 mg, 100 mg, 200 mg CA: 30 mg, 75 mg, I: 25 mg/mL, 1 mL, 2 mL	25–200 mg/day in 2–4 divided doses	2,000 mg/day	Use dosages in the lower ranges with more gradual dosage adjustments.	Use caution.	Use caution.	
Fluphenazine	T: 1 mg, 2.5 mg, 5 mg, 10 mg LAI: 25 mg/mL, I: 2.5 mg/mL E: 2.5 mg/ 5mL CO: 5 mg/mL	2.5–10 mg/day in 3–4 divided doses	20 mg/day	1–2.5 mg daily initial, increase to clinical response	Use caution.	Contraindicated	
Haloperidol	T: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg CO: 2 mg/mL I: 5 mg/mL LAI: 50 mg/mL, 100 mg/mL	2–10 mg/day in 1–3 divided doses	20 mg/day	No adjustment necessary	No adjustment necessary	Use caution.	Haloperidol plasma concentrations might help guide treatment.

[a] U.S. Package Inserts
[b] Daily Med: https://dailymed.nlm.nih.gov
[c] UpToDate: https://uptodate.com
[d] Lexicomp: https://online.lexi.com
[e] Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology 7th edition. New York, NY. Cambridge University Press, 2021.
[f] Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868–872.
[g] Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the therapeutic drug monitoring task force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie and Pharmakopsychiatrie. J Clin Psychiatry 2020;81(3):19cs13169.

Medication	Dosage Form or Forms	Initial Oral Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Loxapine	CA: 5 mg, 10 mg, 25 mg, 50 mg Inh: 10 mg unit in a single-use inhaler	10 mg twice daily	250 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	Inhalation powder must be administered by a health care professional in a setting with immediate onsite access to manage acute bronchospasm.
Molindone	T: 5 mg, 10 mg, 25 mg	50–75 mg/day in 3–4 divided doses	225 mg/day	No adjustment necessary	No adjustment necessary	Use caution.	
Perphenazine	T: 2 mg, 4 mg, 8 mg, 16 mg	8–16 mg/day in divided doses	64 mg/day	No adjustment necessary	Use caution.	Contraindicated	
Pimozide	T: 1 mg, 2 mg	1–2 mg/day in divided doses	4 mg/day** 10 mg/day	1 mg/day initial, gradual dose titration to response	Use caution.	Use caution.	Perform CYP2D6 genotyping for doses > 4 mg/day.
Thioridazine	T: 10 mg, 15 mg, 25 mg, 50 mg, 100 mg	50–100 mg 3 times daily	800 mg/day	No adjustment necessary	No adjustment necessary	Use caution.	Might cause dose-dependent QTc prolongation
Thiothixene	CA: 2 mg. 5 mg, 10 mg	6–10 mg/day in divided doses	60 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	
Trifluoperazine	T: 1 mg, 2 mg, 5 mg, 10 mg	2–5 mg twice daily	40 mg/day	No adjustment necessary	No adjustment necessary	Contraindicated	

Abbreviations: tablet; CO: concentrate; I: injection; LAI: long-acting injection; E: elixir; S: solution; CA: capsule; Inh: inhaler. ** for CYP2D6 poor metabolize

Table 5: Antipsychotic Oral Dosing and Dosage Forms – Second-Generation Antipsychotics[h,i,j,k,l,m,n]

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Aripiprazole	T: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg ODT: 10 mg, 15 mg S: 1 mg/ml LAI (Maintena): 300 mg, 400 mg LAI (Aristada): 441 mg, 662 mg, 882 mg, 1 <064 mg I (single-dose): 675 mg	10 mg or 15 mg once daily	30 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	Dose adjustment is warranted in patients who are CYP2D6 poor metabolizers or taking medications that inhibit or induce CYP3A4.
Asenapine	ST: 2.5 mg 5 mg 1 mg TD: 3.8 mg/24 hours, 5.7 mg/24 hours, 7.6 mg/24 hours	5 mg twice daily (ST) 3.8 mg/day (TD)	10 mg twice daily (ST) 7.6 mg/day (TD)	No adjustment necessary	No adjustment necessary	No adjustment necessary (Child-Pugh A or B) Contraindicated (Child-Pugh C)	Patients may not eat or drink for 10 minutes following sublingual administration. Do not cut the transdermal version; the whole transdermal system should be applied.

h U.S. Package Inserts
i Daily Med: https://dailymed.nlm.nih.gov
j UpToDate: https://uptodate.com
k Lexicomp: https://online.lexi.com
l Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology 7th edition. New York, NY. Cambridge University Press, 2021.
m Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868–872.
n Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the therapeutic drug monitoring task force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie and Pharmakopsychiatrie. J Clin Psychiatry 2020;81(3):19cs13169.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Brexpiprazole	T: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	1 mg once daily	4 mg/day	Use dosages in the lower ranges with more gradual dosage adjustments.	No adjustment necessary (CrCl >60 ml/min) 3 mg once daily initial (CrCl <60 ml/min)	No adjustment necessary (Child-Pugh A) 3 mg once daily initial (Child-Pugh B or C)	Dose adjustment is warranted in patients who are CYP2D6 poor metabolizers or taking medications that inhibit CYP3A4.
Cariprazine	CA: 1.5 mg, 3 mg, 4.5 mg, 6 mg	1.5 mg once daily	6 mg/day	No adjustment necessary	No adjustment necessary (CrCl >30 ml/min) Not recommend- ed (CrCl <30ml/min)	No adjustment necessary (Child-Pugh A or B) Not recommended (Child-Pugh C)	
Clozapine	T: 12.5 mg, 25 mg scored, 50 mg scored, 200 mg ODT: 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg SU: 50 mg/mL	12.5 mg once or twice daily	900 mg/day	Use dosages in the lower ranges with more gradual dosage adjustments.	Use caution.	Use caution.	If treatment lapses >48 hours, re-titrate at initial doses. Clozapine plasma concentrations may be used to guide treatment.
Iloperidone	T: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg	1 mg twice daily	24 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary (mild) Use caution. (moderate) Not recommended (severe)	The dose should be reduced initially in patients who are poor metabolizers of CYP2D6.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Lumateperone	CA: 42 mg, 21 mg, 10.5 mg	42 mg once daily	42 mg/day, 21 mg/day (moderate CYP3A4 inhibitor) 10.5 mg/day (strong CYP3A4 inhibitor)	No adjustment necessary	No adjustment necessary	No adjustment necessary (Child-Pugh A) 21 mg/day (Child-Pugh B and C)	Avoid concomitant use with strong CYP3A4 inducers.
Lurasidone	T: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg	40 mg once daily	160mg/day	No adjustment necessary	CrCl >50 ml/min: No adjustment necessary CrCl <50 ml/min: 20 mg once daily initial	No adjustment necessary (Child-Pugh A) 20 mg daily initial (Child-Pugh B or C)	Take within 30 minutes of food intake (>350 calories). Avoid concomitant use with strong CYP3A4 inhibitors and inducers.
Olanzapine	T: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg ODT: 5 mg, 10 mg, 15 mg, 20mg I: 5 mg/mL each vial contains 10 mg LAI: 210 mg, 300 mg, 405 mg	5–10 mg once daily	20 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	Use of parenteral benzodiazepines with short-acting IM olanzapine is not recommended. Long-acting dosage form associated with post-injection delirium/sedation syndrome.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Olanzapine/ Samidorphan	T: Olanzapine 5 mg /Samidorphan 10 mg, Olanzapine 10 mg /Samidorphan 10 mg, Olanzapine 15 mg /Samidorphan 10 mg, Olanzapine 20 mg /samidorphan 10 mg	5/10 mg or 10/10 mg once daily	20/10 mg once daily	Use caution.	No adjustment necessary (CrCl >15 ml/min) Not recommended (CrCl<15 ml/min)	Use caution.	Concomitant use with opioids and in patients undergoing acute opioid withdrawal is contraindicated.
Paliperidone	ET: 1.5 mg, 3 mg, 6 mg, 9 mg 1-month Injection: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg 3-month Injection: 273 mg, 410 mg, 546 mg, 819 mg 6-month Injection: 1,092 mg, 1,560 mg	6 mg once daily	12 mg/day	Use caution.	3 mg once daily initial (CrCl 50–79 ml/min) 1.5 mg once daily initial (CrCl 10–49ml/min) Not recommended (CrCl < 10 ml/min)	No adjustment necessary	
Quetiapine	T: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg ET : 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	25 mg twice daily (T) 300 mg once daily (ET)	800 mg/day	50 mg/day initial	No adjustment necessary	25 mg/day (T) initial, increase based on response and tolerability 50 mg/day (ET) initial, increase based on response and tolerability	

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Risperidone	T: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg ODT: 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg S: 1 mg/mL–30 mL bottle LAI (Consta): 12.5 mg vial/kit, 25 mg vial/kit, 37.5 mg vial/kit, 50 mg vial/kit LAI (Perseris): 90 mg, 120 mg	1–2 mg/day in 1 or 2 divided doses	16 mg/day (package insert) 6–8 mg/day (clinical practice)	0.5 mg twice daily initial	No adjustment necessary (CrCl >60 ml/min) 50%–75% of the usual dose (CrCl 30–60 ml/min) 50% of the usual standard dose (CrCl 10 to <30 ml/min)	No adjustment necessary (Child-Pugh A or B) 0.5 mg twice daily (Child-Pugh C)	6–8mg/day is the usual maximum dose.
Ziprasidone	CA: 20 mg, 40 mg, 60 mg, 80 mg I: 20 mg/mL	20–40 mg twice daily with a meal	80 mg twice daily	No adjustment necessary	No adjustment necessary	Use caution.	Administer with a meal (>500 calories).

Abbreviations: T: tablet; CO: concentrate; I: injection; LAI: long-acting injection; E: elixir; S: solution; CA: capsule; ODT: oral disintegrating tablet; TS: tablet with sensor; TD: transdermal; ST: sublingual tablet; SU: suspension; ET: extended-release tablet; CrCl: creatinine clearance; ml/min: milliliters/minute

Table 6: Antipsychotic Adverse Event Profiles[o,p,q,r,s,t,u]

Medication	EPS	Sedation	Weight Gain	Metabolic	Orthostasis	AcH	QTc
Aripiprazole	++	+/0+	+/0+	+/0+	+	0	+
Asenapine	++	+	+	+	+	0	+
Brexpiprazole	++	+	0	+	+	0	+
Cariprazine	++	+	+	+	+	0	+
Chlorpromazine	++	+++	+++	++	+++	+++	++
Clozapine	+0	+++	+++	+++	+++	+++	++
Fluphenazine	+++	+	+	+	+	0	+
Haloperidol	+++	+	+	+	+	0	++
Iloperidone	+	+	++	+	+++	0	++
Loxapine	++	+	+	+	+	+	+
Lumateperone	+	+	0	+	+	+	+
Lurasidone	++	+	+	+	+	0	+
Molindone	++	++	+	+	+	+	+
Olanzapine	+	+++	+++	+++	++	++	++
Olanzapine/ Samidorphan	+	+++	++	+++	++	++	++
Paliperidone	+++	+	++	+	+	+	+
Perphenazine	++	+	++	+	++	0	+
Pimavanserin	0	+	0	0	+	++	+
Pimozide	+++	+	+	+	++	0	++
Quetiapine	+	+++	++	++	++	+	++
Risperidone	+++	+	++	++	++	0	++
Thioridazine	+	+++	++	+	+++	+++	+++
Thiothixene	+++	+	+	+	++	0	+
Trifluoperazine	+++	+	+	+	++	0	+
Ziprasidone	++	+	+	+	++	0	+++

Key: +++ = strong effect; ++ = moderate effect; + = minimal effect; 0 = no effect

Abbreviations: EPS=extrapyramidal side effects; Metabolic=diabetes, dyslipidemia, increased waist circumference; AcH=anticholinergic effects; QTc=QTc prolongation

[o] U.S. Package Inserts
[p] Daily Med: https://dailymed.nlm.nih.gov
[q] UpToDate: https://uptodate.com
[r] Lexicomp: https://online.lexi.com
[s] Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology 7th edition. New York, NY. Cambridge University Press, 2021.
[t] Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868–872.
[u] Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the therapeutic drug monitoring task force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie and Pharmakopsychiatrie. J Clin Psychiatry 2020;81(3):19cs13169.

Table 7: Drugs Used to Treat Antipsychotic Associated Adverse Effects[v,w,x,y,z,aa,bb]

Medication	Initial Oral Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Amantadine	100 mg twice daily 129 mg once daily (ET)	400 mg/day 322 mg/day (ET)	No adjustment necessary	200 mg x 1 then 100 mg/day (CrCl 30–50 ml/min) 200 mg x1 then 100 mg every other day (CrCl 15–29 ml/min) 200 mg every 7 days (CrCl <15 ml/min)	No adjustment necessary	It may be used for drug-induced parkinsonism, neuroleptic malignant syndrome, or tardive dyskinesia.
Benztropine	1–2 mg/day	6 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	It may be used for acute dystonia and drug-induced parkinsonism.
Clozapine	12.5 mg once or twice daily	900 mg/day	Use dosages in the lower ranges with more gradual dosage adjustments.	Use caution	Use caution.	It may be used to treat tardive dyskinesia.
Deutetrabenazine	6 mg twice daily	48 mg/day	No adjustment necessary	Use caution	Contraindicated	Indicated for tardive dyskinesia

v U.S. Package Inserts
w Daily Med: https://dailymed.nlm.nih.gov
x UpToDate: https://uptodate.com
y Lexicomp: https://online.lexi.com
z Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology 7th edition. New York, NY. Cambridge University Press, 2021.
aa Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868–872.
bb Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the therapeutic drug monitoring task force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie and Pharmakopsychiatrie. J Clin Psychiatry 2020;81(3):19cs13169.

Medication	Initial Oral Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Diphenhydramine	25–50 mg	300 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	It may be used for acute dystonia, drug-induced parkinsonism, and clozapine-induced sialorrhea.
Metformin	250–500 mg twice daily	2 g daily in 2 or 3 divided doses	No adjustment necessary	CrCl >45 ml/min, no adjustment necessary CrCl <45 ml/min, not recommended	Avoid use.	It may be used for antipsychotic-induced weight gain.
Propranolol	10 mg twice daily	120 mg/day	No adjustment necessary	Use caution.	Use caution.	It may be used for akathisia
Pyridoxine	400 mg/day	1,200 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	It has been used as a treatment for tardive dyskinesia
Tetrabenazine	50 mg/day in divided doses	150 mg/day in divided doses	No adjustment necessary	Use caution.	Contraindicated	It may be used to treat tardive dyskinesia
Topiramate	50 mg/day	200 mg/day	50% of usual adult dosage	CrCl ≥70 ml/min, no adjustment necessary CrCl <70 ml/min, reduce dose 50%	Use caution.	It may be used for antipsychotic-induced weight gain
Trihexyphenidyl	1 mg/day	15 mg/day in 3 or 4 divided doses	Avoid use.	Use caution.	Use caution.	Indicated for dystonia and parkinsonism

Medication	Initial Oral Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Valbenazine	40 mg once daily	80 mg once daily	No adjustment necessary	No adjustment necessary	No adjustment necessary (Child-Pugh A) 40 mg once daily (Child-Pugh B or C)	Indicated for tardive dyskinesia

Abbreviations: T: tablet; I: injection; P: powder; E: elixir; S: solution; CA: capsule; ODT: oral disintegrating tablet; SU: suspension; ET: extended-release tablet; EC: extend-release capsule; CrCl: creatinine clearance; IU: international unit

Table 8: Metabolic Monitoring

	Baseline	1 Month	2 Months	3 Months	6 Months	Annually
Body Mass Index	X	X	X	X	X	X
Waist Circumference	X			X		X
HbA1c	X			X		X
Fasting Plasma Glucose	X			X		X
Fasting Lipid Panel	X			X		X

Table 9: Antipsychotic Long-Acting Injectable[cc,dd,ee,ff,gg,hh,ii,jj]

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
First-Generation Antipsychotics	***Fluphenazine decanoate***	• Deltoid or gluteal • Z track technique	1.25x oral daily dose every 2 weeks	6.25–25 mg every 2 weeks	100 mg every 2 weeks	1–2 weeks
	Haloperidol decanoate	• Deltoid or gluteal • Z track technique	• Loading dose: 20x oral daily dose • Conventional dosing: 10–15x oral daily dose If injection dose conversion is >100, a second injection should be administered in 3–7 days.	• Conventional dosing: Maintain the initial dose. • Loading dose: Maintain the initial dose, which may be decreased by 25% after stabilization.	450 mg q 4 weeks	Not necessary with a loading dose Continue oral dose for 2–3 months with conventional dosing.

[cc] U.S. Package Inserts
[dd] Daily Med: https://dailymed.nlm.nih.gov
[ee] UpToDate: https://uptodate.com
[ff] Lexicomp: https://online.lexi.com
[gg] Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology 7th edition. New York, NY. Cambridge University Press, 2021.
[hh] Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868–872.
[ii] Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the therapeutic drug monitoring task force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie and Pharmakopsychiatrie. J Clin Psychiatry 2020;81(3):19cs13169.
[jj] Oral overlap refers to the need to continue treatment with the oral antipsychotic while awaiting the long-acting injectable's effects.

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics	***Aripiprazole monohydrate***	Deltoid or gluteal	• 400 mg/month • 300 mg/month (known CYP2D6 poor metabolizer)	• 400 mg/month • 300 mg/month (known CYP2D6 poor metabolizer) • 200 mg/month (CYP2D6 poor metabolizers taking concomitant CYP3A4 inhibitors)	• 400 mg/ month • 300 mg/ month (known CYP2D6 poor metabolizer)	14 consecutive days of concurrent oral aripiprazole
	Aripiprazole lauroxil	Gluteal 441 mg dose may be given in the deltoid	• 10 mg/day=441 mg • 15 mg/day=662 mg/month • 882 mg/6 weeks, OR • 1,064 mg/2 months • >/= 20 mg/day=882 mg/month	• 441–882 mg/month • 882 mg every 6 weeks • 1,064 mg every 2 months	882 mg/month	In conjunction with the first dose, take 21 consecutive days of concurrent oral aripiprazole.
	Olanzapine pamoate	Gluteal	• 10 mg/day oral= 210 mg every 2 weeks x 4 doses OR 405 mg every month x 2 doses • 15 mg/day oral= 300 mg every 2 weeks x 4 doses • 20 mg/day oral= 300 mg every 2 weeks	• 10 mg/day oral= 150 mg every 2 weeks OR 300 mg every month • 15 mg/day oral= 210 mg every 2 weeks OR 405 mg/month • 20 mg/day oral= 300 mg every 2 weeks	300 mg every 2 weeks OR 405 mg every month	Oral overlap is not required. Associated with a REMS program

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics (cont.)	***Paliperidone palmitate (PP1M)***	Initial: deltoid Maintenance: deltoid or gluteal	234 mg followed by 156 mg 1 week later (+/- 4 days)	39 mg–234 mg every month Dose conversion: • 12 mg oral = 234 mg/ month • 9 mg oral = 156 mg/ month • 6 mg oral = 117 mg/ month • 3 mg oral = 39–78 mg/ month	234 mg/month	Not required
	Paliperidone palmitate Q3 MO (PP3M)	Deltoid or gluteal	To be used only after paliperidone palmitate has been established as adequate treatment for at least 4 months, with the last 2 doses being the same strength • 78 mg PP1M = 273 mg • 117 mg PP1M = 410 mg • 156 mg PP1M = 546 mg • 234 mg PP1M = 819 mg	• 273 mg–819 mg every 3 months	819 mg every 3 months	Not required

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics (continued)	***Paliperidone palmitate Q6 MO (PP6M)***	Gluteal	To be used only after paliperidone palmitate has been established as adequate treatment for at least 4 months or PP3M for at least one 3-month cycle • 156 mg PP1M = 1,092 mg • 234 mg PP1M = 1,560 mg • 546 mg PP3M = 1,092 mg • 819 mg PP3M = 1,560 mg	• 1,092 mg–1,560 mg every 6 months	1560 mg every 6 months	Not required
	Risperidone long-acting injection	Deltoid or gluteal	25 mg every 2 weeks	• 25–50 mg every 2 weeks • 1–3 mg PO=25 mg • 4–5 mg PO=37.5 mg • >6 mg PO=50 mg • Consider 12.5 mg for history of poor tolerability or renal or hepatic impairment.	50 mg every 2 weeks	Oral overlap with risperidone or another antipsychotic should occur for at least 21 days after the first injection.

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics (cont.)	***Risperidone subcutaneous***	Subcutaneous abdomen tissue	3 mg oral risperidone= 90 mg SQ 4 mg oral risperidone= 120 mg SQ Patients on stable risperidone doses lower than 3 mg/day or more than 4 mg/day might not be candidates for risperidone SQ.	90–120 mg	120 mg	Not required

Methods

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.[2] The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).[3] Appendix A in the full VA/DoD Schizophrenia CPG provides a detailed description of the CPG development methodology.

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to craft each recommendation and determine its strength. Per GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation: confidence in the quality of the evidence, balance of desirable and undesirable outcomes, patient values and preferences, other considerations as appropriate (e.g., resource use, equity) (see Grading Recommendations in the full VA/DoD Schizophrenia CPG).[4]

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.[5] A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see Table 10).

Table 10. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

The GRADE of each recommendation made in the 2023 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A in the full VA/DoD Schizophrenia CPG.

References

1. Evidence based practice work group charter. https://www.healthquality.va.gov/documents/EvidenceBasedPracticeWGCharter123020161.pdf. Updated January 9, 2017.
2. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. Med Decis Making. Apr-Jun 1992;12(2):149-154. PMID: 1573982.
3. U.S. Department of Veteran Affairs, Department of Defense. Guideline for guidelines. Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup; Revised January 29, 2019.
4. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. J Clin Epidemiol. Jul 2013;66(7):719-725. PMID: 23312392.
5. The guidelines manual. London: National Institute for Health and Care Excellence;2012. http://www.nice.org.uk/article/pmg6/resources/non-guidance-the-guidelines-manual-pdf.
6. Martinez Garcia L, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. Implement Sci. 2014;9:72. PMID: 24919856.
7. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: definitions and applications to improve outcomes. J Am Acad Nurse Pract. Dec 2008; 20(12):600-607. PMID: 19120591.
8. Stewart M, Brown JB, Donner A, et al. The impact of patient-centered care on outcomes. J Fam Pract. Sep 2000;49(9):796-804. PMID: 11032203.
9. Crossing the quality chasm: A new health system for the 21st century. Washington DC: National Academies Press;2001.

Access to the full guideline and additional resources is available at: https://www.healthquality.va.gov/.