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

Department of Veterans Affairs
Department of Defense

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 2.0 – 2023

Prepared by

Management of First-Episode Psychosis and Schizophrenia Work Group

With support from

Office of Quality and Patient Safety, Veterans Health Administration

and

Clinical Quality Improvement Program, Defense Health Agency

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I. 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).

II. Background

A. Description of Schizophrenia

Schizophrenia is a neurodevelopmental disorder, such that there is a "**pandysmaturation**," with language and motor delays in childhood, premorbid attentional problems, and often mild social impairment.(2) In adolescence and young adulthood, there is typically a prodromal period of months to years marked by major deficits in attention, social withdrawal, function decline, and emergence of subthreshold psychotic symptoms.(3) The development of threshold psychotic symptoms often occurs in the context of a life change or stressor, which might be relevant to young adult Veterans returning to the United States (U.S.) who can have prodromal symptoms or a first episode of psychosis (FEP).

Schizophrenia impacts many areas of an individual's life, bringing about deficits in perceptual, motor, cognitive, and emotional functioning.(3) Perceptual deficits (commonly called **positive symptoms**) involve distortions in the reception of stimuli, such as hallucinations and delusions. Motor deficits include unnatural postures, positions of the head and shoulders, or involuntary movements of the face and extremities.(4) **Negative symptoms**, referred to as deficit symptoms, cluster into two main components: diminished emotional expression and severe reduction in goal-directed activities because of lack of interest or drive.(3, 5, 6) Negative symptoms are

associated with detrimental effects on an individual's clinical and functional outcomes and QoL.(4) Thus, **negative symptoms are the strongest predictor of poor long-term functioning and predict a chronic course of illness**.(7)

Cognitive dysfunction is a core feature of schizophrenia, observed much earlier in the course of the disorder and before the onset of psychotic symptoms.(6) **The cognitive impairments experienced by individuals with schizophrenia include non-social cognitive domains and social cognitive domains.**(6) Non-social cognitive deficits broadly describe neurocognitive domains with difficulties in thinking, expressing thoughts, attention impairments, working memory, reasoning, and executive functioning.(3, 5) More prominent deficits are seen in cognitive processing speed and verbal memory.(4) Neurocognitive deficits are a significant predictor of functional outcomes in schizophrenia and negatively impact an individual's ability to perform everyday functional skills that allow for independent living, engaging in productive activities, and work performance—further contributing to the disabling nature of the disorder.(6) Early interventions targeting these deficits can be crucial to preventing chronic disability.(5)

Social cognition broadly describes an individual's ability to identify and interpret other's emotions or intentions and use those social signals to guide informed conclusions or behaviors.(6) Social cognitive deficits are observed in emotional expression, emotional experience, and emotion recognition.(8) Social cognitive deficits can negatively impact real-life social situations. Psychosocial dysfunction leads to a decrease in life independence and quality of life (QoL).(4) Addressing psychosocial dysfunction early and consistently throughout treatment can improve interpersonal relationships (i.e., with the family system), subjective perceptions of QoL and illness burden, self-esteem, and self-efficacy.(4, 6) Psychoeducation for individuals and families members' increases knowledge, promotes understanding and acceptance, and decreases stigmatization.(4) The experience of stigmatizing attitudes toward people with schizophrenia is common and might be internalized, leading to "self-stigma."(9) Associated with poorer response to vocational rehabilitation, internalized stigma is a predictor of decreased treatment adherence.(9) Social skill trainings have shown to improve social functioning and perceptions of disease burden.(4)

A diagnosis of schizophrenia does not encompass all clinical presentations of psychotic symptoms. Performing a thorough medical evaluation and considering other psychiatric disorders that might present with psychosis, such as mood substance-related disorders and medical conditions, is essential.(9) No single case is identified for the development of schizophrenia; rather, it is thought that interactions among genes, environment, and psychosocial factors might cause schizophrenia.(9) Heavy use of cannabis is associated with an elevated risk.(9) Though schizophrenia is a long-term condition, symptom resolution proceeds to remission in many patients.(10) In a 2007 naturalistic cohort study, 21% of patients achieved remission with treatment within a year, and a

2008 retrospective observational study measured a 60% remission rate by three years.(10)

B. Epidemiology and Impact on the General Population

Globally, 24 million people (1 in 300) are living with schizophrenia.(11) Measuring the prevalence of schizophrenia is difficult because of the complexity of the diagnosis, the existence of co-occurring conditions, and the differing methods for diagnosis and case identification, but it is estimated at approximately 1% of the population.(12)

The typical age of onset is in late adolescence or early adulthood with prevalence peaking at age 40. Childhood-onset and onset beyond age 45 are uncommon. The age of onset in men is usually between 18 and 25, and in women onset occurs between age 25 and 30. A slightly higher prevalence occurs in men than in women, and the prognosis is worse in men.

Schizophrenia is one of the top 15 leading causes of disability worldwide.(13) The 25–54 age group observed the most significant illness burden, losses in productivity, compounded by out-of-pocket cost for treatment and often leading to significant high financial costs and burdens on the health care and welfare systems.(14) In the U.S., individuals living with schizophrenia are also two to three times more likely to die prematurely than the general population, with individuals dying an average of 15 years sooner.(15) Schizophrenia is linked to higher rates of co-occurring medical conditions, potentially related to under-detection and under-treatment of underlying physical illnesses, especially chronic diseases such as coronary heart disease, stroke, type 2 diabetes, respiratory diseases, and some cancers (14). Nearly 50% of individuals diagnosed with schizophrenia have co-occurring mental or behavioral health disorders.(16) Other contributory factors include prevalent tobacco use in schizophrenia and possibly the effects of antipsychotic medications themselves.

Individuals with schizophrenia face also other challenges because of the large stigma surrounding this demographic. Schizophrenia can cause social challenges resulting in social exclusion and strained relationships with family and friends. At a larger scale, this stigma perpetuates the discrimination against individuals with schizophrenia, thus negatively impacting their access to education, health care, employment, and housing.(17)

C. Schizophrenia across the Lifespan in the Department of Veterans Affairs Health Care Population

Information on the demographic and clinical characteristics of Veterans treated for schizophrenia in the VA health care system and their use of clinical services was obtained specifically to support the development of this CPG from the administrative data included in the National Psychosis Registry and related data sources maintained by the VA Office of Mental Health and Suicide Prevention.(18)

a. Demographics

In fiscal year (FY) 2021, VA provided health care for 73,867 Veterans with schizophrenia, 90.3% being men and 9.7% being women. Of these individuals, 7.5% were under age 35, 15.0% were age 35–49, 35.1% were age 50–64, 39.5% were age 65–79, and 2.9% were age 80 and older. Additionally, 54.5% were White, 35.4% were Black or African American, 1.3% were Asian, 0.8% were Native American or Alaskan Native, 1.0% were multiracial, and 7.1% were from other or unknown races. Individuals of Hispanic ethnicity made up 9.0%. Finally, 68.4% had some degree of service-connected disability.

b. Clinical Characteristics

Most of the Veterans treated for schizophrenia in VA had co-occurring conditions or complications. Based on administrative data derived from electronic medical records, 22.4% had a coexisting diagnosis of post-traumatic stress disorder (PTSD), and 28.0% had a substance use disorder (SUD). In addition, 20.6% had a diagnosis of a tobacco-use disorder; however, actual rates for tobacco use are likely higher. Co-occurring medical conditions were also common. Nearly half (49.5%) had hypertension, 30.5% had diabetes, and 6.5% had heart failure. The average body mass index (BMI) was 29.8, indicating that a sizeable proportion were overweight or obese. During FY2021, 4.1% of VA patients with schizophrenia died. After controlling for age, sex, and overall medical comorbidity, the all-cause mortality rate for VA patients with schizophrenia and other psychotic disorders (including schizoaffective and bipolar disorders) was 71% greater than for VHA users without a mental health condition.(19)

c. Service Use

In FY2021, 10.2% of individuals with schizophrenia receiving treatment through VA were treated in a VA inpatient mental health unit. In that year, 65.5% were treated in VA general mental health clinics with an average of 12.5 visits during the year. 2.5% received supported employment services; 10.2% were treated in Intensive Community Mental Health Recovery (ICMHR) programs (e.g., intensive case management); 5.5% were seen in Psychosocial Recovery and Rehabilitation Centers offering intensive rehabilitation programming; and 11.1% received homeless services. 3.9% were recognized and flagged as being at high risk for suicide, and 3.1% had medical record flags for disruptive behavior. In addition, 12.9% of individuals with schizophrenia were treated in a VA inpatient medical or surgical unit during the year; 74.3% received primary care services from VA; and 33.8% were seen in VA emergency departments for mental health or medical or surgical problems. In 2021, 71.3% of VA individuals with schizophrenia filled one or more VA prescriptions for oral antipsychotic medications, and 20.4% received at least a single dose of a long-acting injectable antipsychotic medication. Of these individuals receiving oral antipsychotics, 77.4% received prescriptions for a single agent; 19.2% for two; and 3.6% for three or more. Finally, 4.8% received a prescription for clozapine.

d. Early Episode Psychoses

VA administrative records do not allow for a distinction between individuals with a true first episode of a psychotic disorder versus individuals who sought care after receiving treatment for previous episodes in other systems. Based on this limitation, we define individuals with early episode psychoses as those who have a relevant International Classification of Diseases-10 (ICD-10) diagnosis associated with a clinical encounter and no such diagnosis in the previous three years who are of age less than or equal to 30.(20) Here, we report on early episodes, rather than FEPs. In a typical year, 4.1% of the Veterans treated in VA for a psychotic disorder, independent of diagnosis, were individuals experiencing an early episode.(20)

Veterans with early episodes were younger than other Veterans with psychoses (average age 26.6 versus 58.7) but similar in terms of sex, race, and the level of service-connected disability. Rates for PTSD (41.3%) and SUD (48.1%) comorbidities were greater for early episode patients than for others with psychotic disorders, but the proportion with diagnosed general medical conditions was lower, consistent with their younger age. The proportions of those receiving inpatient care (32.0%), those recognized and flagged as being at high risk for suicide (13.9%), and those receiving services to address homelessness (19.6%) were greater for early episodes.

In recognition of the specific needs of Veterans with early episode psychoses and of the value of Coordinated Specialty Care (CSC), VA established the Early Psychosis Intervention Coordination (EPIC) program in 2020.(21) The program requires each VA Medical Center to establish EPIC coordinators and clinical teams to ensure Veterans with early episodes of psychosis have access to coordinated services that include the basic components of care offered in CSC programs. These basic components of care include evidence-based pharmacologic treatment and psychosocial services such as supported employment and educational services, cognitive therapy, individual resiliency training, family support, psychoeducation about mental illness for the Veterans and families, and other therapies as needed by the individual, including treatment for coexisting conditions such as SUD.

e. Schizophrenia in Late Life

Of the individuals with schizophrenia who receive care in VA, 42.5% are age 65 or older. In general, late-life schizophrenia represents a heterogeneous mix of patients who differ in the age of onset for their condition.(22) They include individuals with an early onset who have grown older with the condition (given that schizophrenia and other psychotic disorders are associated with substantial increases in mortality, these individuals might be considered survivors); individuals with late-onset schizophrenia, with initial onset after age 40, who might experience lower levels of positive symptoms; and those with very late-onset schizophrenia-like illness, who might experience lower levels of negative symptoms. Remission in later life is possible for individuals with schizophrenia, and providers should be alert to the possibility that new opportunities for

rehabilitation might emerge as people grow older. However, in general, the clinical course of the disease in late life is highly variable.(23, 24)

In general, older individuals with schizophrenia exhibit mildly progressive declines in cognition(25); however, rates for medical record diagnoses of dementia, based on claims data, show a substantially increased rate with age.(26) Taken together, these findings support the value of monitoring cognitive functioning and for ensuring that increased impairments are evaluated with care.

One possibly reversible source of cognitive decline might be related to increased sensitivity to the cognitive effects of anticholinergic medication in older individuals. Other reversible sources of suffering and impairment include depression and pain, both common in late-life schizophrenia as well as in other elderly people.(27)

Medical comorbidities are common in these individuals and include those related to long-term exposures to psychopharmacologic treatment; to the “wear and tear” conditions that accumulate with aging; and, possibly, to what has been considered to be “accelerated aging” in schizophrenia.(28) As a result, older patients with schizophrenia are likely to be seen across the full range of medical, surgical, rehabilitative, and long-term care services. As a result, it might be useful to provide care management to coach patients on how to interact with staff to help ensure their needs are met and to educate providers in these services about working with patients with schizophrenia.

f. Summary

Overall, Veterans with schizophrenia receiving medical care in VA are likely to be middle-aged or elderly: 77.5% are age 50 or older, and 42.4% are age 65 and older. They experience high degrees of co-occurring mental health conditions, primarily from PTSD and SUDs, and high degrees of medical comorbidity, primarily related to obesity, hypertension, and diabetes. A substantial proportion has been diagnosed with a tobacco use disorder. Most of the individuals treated for schizophrenia in VA receive both primary care and mental health services from VA. Therefore, VA has both the need and the opportunity to treat the Veterans’ schizophrenia in the context of aging and co-occurring mental health and medical conditions.

Veterans with early episode psychoses represented 4.1% of those treated in VA for a psychotic disorder. They experience PTSD, SUD, risks for suicide and homelessness, and the need for inpatient mental health care more frequently than others with psychotic disorders. To address their needs, VA requires that specific early episode programs must be available at each of its medical centers.

D. First-Episode Psychosis and Prodromal Syndromes in the Department of Defense Population

Active duty Service members have several risk factors for prodromal syndromes and FEP related to developmental, situational, and occupational factors. Some of these

factors include age, separation from primary support systems, and exposure to the physical and psychological stressors of training and active duty military service.

According to the DSM-5, the peak age of onset in the general population occurs between the early to mid-20s for males and late-20s for females.(29) A recent report by DoD covering calendar years 2018–2020 estimated the prevalence of FEP among U.S. active duty Service members to be 95 per 100,000. Of the 3,943 cohort members in the study period, 57% (2,320) were separated from service by one year of the initial diagnosis.(30)

Recognition of prodromal syndromes and FEP in military populations is critical because effective management of these conditions could have a substantial downstream impact on the severity and progression of psychiatric illness later in life. As of the writing of this CPG, no standard early intervention and treatment protocol exists for those individuals in the DoD military system. In addition to the long-term benefits of early intervention for the Service member and improved mission readiness for the military, effective treatment will lead to a lessened financial burden to both the military and Veteran health care systems. The financial burden to the military health care system regarding the treatment of these disorders is related to hospitalization and medical treatment, housing, operational unit readiness, and potential degradation of the mission.

E. Recovery Movement

a. Mental Health Recovery and This Clinical Practice Guideline

The term “recovery” has multiple meanings. The earliest definition of recovery is akin to remission and is used to indicate the end of an episode of illness, the elimination of symptoms of a particular illness, or both. Similarly, in SUD contexts, recovery is often equated with abstinence from substances and is common parlance within 12-step programs such as Alcoholics Anonymous. The term “mental health recovery” has evolved from these earlier definitions and is defined as an orientation or a process in which individuals living with psychiatric disabilities, such as schizophrenia, live meaningful lives in their community of choice despite the presence of psychiatric symptoms and deficits.(31) Recovery has been described as both an individual and system-level orientation, but this review will focus on the individual, given the context of CPGs.(32) The concept of mental health recovery is critically important because it relates to the orientation to wellbeing as well as the care process of individuals living with schizophrenia and their families.

This CPG aims to provide recommendations to support the mental health recovery of individuals with schizophrenia; however, the recommendations only partially capture the range of current research and other scholarship in this area. This brief overview of mental health recovery provides a broader orientation as to how mental health services might support individuals with schizophrenia beyond the scope of these CPG

recommendations and outlines some of the limitations of this CPG process in understanding and promoting recovery in schizophrenia.

b. What Is Mental Health Recovery?

The Substance Abuse and Mental Health Services Administration (SAMHSA) developed this working definition of recovery: "A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential." This definition includes 10 guiding principles.(33)

1. Recovery emerges from hope.
2. Recovery is person driven.
3. Recovery occurs via many pathways.
4. Recovery is holistic.
5. Recovery is supported by peers and allies.
6. Recovery is supported through relationships and social networks.
7. Recovery is culturally based and influenced.
8. Recovery is supported by addressing trauma.
9. Recovery involves individual, family, and community strengths and responsibility.
10. Recovery is based on respect.

Various other recovery frameworks have been developed. One popular framework identifies five recovery processes: Connectedness, Hope and Optimism, Identity, Meaning in Life, and Empowerment (CHIME).(34) CHIME was developed as part of a systematic review (SR) and narrative synthesis of 97 conceptual models of recovery. A more recent scoping review of SRs and meta-analyses of recovery models found support for some elements of the CHIME framework. However, they noted that conceptualizations of recovery have changed over time, proposing that some new elements should be added to CHIME and others should be de-emphasized, suggesting that recovery is a dynamic concept.(35)

Dell et al. (2021) conducted a review of SRs of models of mental health recovery to use as the basis for a thematically generated recovery model.(36) Five themes were identified, beginning with "(a) Recovery is a process of overcoming despair to realize a positive sense of self and well-being. . . . The remaining four themes outlined the factors and experiences that were most associated with recovery . . . including: (b) environmental requirements necessary for recovery; (c) the role of autonomy, control, and personal responsibility; (d) the importance of social support and meaningful activities to the development of a sense of belonging and purpose; and (e) developing acceptance of one's illness and insight into how to establish and maintain wellness."

As demonstrated by these multiple frameworks, no consensus on a single definition of recovery exists. Recovery is an inherently individualistic concept subject to personal and professional interpretation and, therefore, impossible to define systematically. This fact makes incorporating the recovery concept as an outcome in SRs and CPGs, such as this one, challenging.

c. What Is the Recovery Movement?

The recovery movement has shaped the philosophy and service delivery of modern mental health care. The origins of the recovery movement can be traced to the social justice movements of the 1960s and 1970s led by ex-patient and survivor activist groups. These groups expressed outrage about their shared experiences within the mental health system. They worked to develop support networks and to elevate their voices separate from the mainstream, professional mental health providers.(37) These efforts were centered in social justice and, largely, rejected professional intervention.(38)

Although the meaningful influence of the recovery movement has been debated by some (e.g., Braslow et al. [2013]),(39) others believe the movement has led to changes in the professionals' and institutions' approach reflected in policy and programming for mental health in the U.S. today. These changes include VHA's longstanding commitment to transforming mental health to include a continuum of recovery-oriented and psychosocial rehabilitation services that facilitate a journey of healing and promote the pursuit of personal and meaningful goals for individuals living with psychiatric disabilities.(40) Proponents believe the recovery movement has influenced service delivery, helping shape new and re-imagined interventions to support recovery goals, such as in incorporating Wellness Recovery Action Planning, Illness Management and Recovery, Integrated Peer Support services (of note, VA employs more than 1,100 Certified Peer Specialists trained to use their own lived experience with mental health challenges to help other Veterans), and supported employment. Recovery has been featured in influential U.S. government documents (41) and is visible in governmental agencies, such as SAMHSA's recent creation of an Office of Recovery.(33) Further, the mental health care system has seen increased adoption of pragmatic, non-theoretical psychiatric rehabilitation practices that focus on improving life roles or community status (e.g., employment, housing, friendship, leisure activities, self-care, wellness management) as well as the development of treatments that target functioning and other non-symptom domains. Some of these recovery-focused treatments are not included in this CPG, for several reasons: the Work Group had a limited number of key questions that could be asked because of methodological challenges in measuring and studying recovery and because of a lack of alignment between the CPG protocols and the existing evidence base as further described in the subsection below.

d. Challenges in Incorporating Recovery into This Guideline

The inherently individual and philosophical nature of recovery allows individuals with psychiatric disabilities to personalize their recovery experience.(42) Although potentially beneficial in clinical practice, this lack of consistent operationalization leads to challenges in amassing systematic evidence supporting the recovery concept. The diversity of definitions leads to a range of measures and measurement approaches adopted by researchers. For example, some have attempted to define and measure the concept of recovery to be used as outcome measures in studies.(43-46) In contrast, others have focused on hypothesized components, such as QoL, empowerment, hope, functioning (including role functioning), and other domains.(47) Nonetheless, the studies reviewed in this CPG rarely include definitions and measures of recovery and related domains that could be meaningfully combined to draw conclusions about the effect of these interventions on recovery, and, thus, these concepts are largely absent from the recommendation discussions.

Further, challenges occurred in delineating the full range of evidence about interventions designed to promote recovery in this CPG. The systematic evidence review for this CPG included only studies of individuals with schizophrenia or schizoaffective disorder and excluded studies in which participants were diagnostically heterogeneous, such as those described as having a severe mental illness in which schizophrenia was just one inclusion criterion (see Appendix A). The Work Group could not consider studies of interventions designed to improve recovery-oriented domains such as housing, employment, social connectedness, peer support, and other pragmatically oriented psychiatric rehabilitation interventions if they did not contain a majority of individuals with diagnoses of schizophrenia. As a result, this CPG does not reflect all the available research on practices designed to promote recovery. This circumscription limited the Work Group's ability to understand how existing interventions might promote recovery for individuals with schizophrenia. Research on heterogeneous populations is often an appropriate way to develop evidence on recovery-promoting interventions. When symptoms are not the primary target of the intervention, testing interventions on diagnostically narrow groups might be unnecessary. However, the large body of evidence on recovery-oriented treatments conducted with diagnostically diverse individuals could not be included here because of the diagnostically homogeneous protocols adopted by the CPG, which might have influenced the Work Group's ability to make recommendations on recovery-oriented treatments.

III. Scope of This Guideline

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 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).

A. Guideline Audience

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.

B. Guideline Population

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.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline

This document is the first version of the VA/DoD Schizophrenia CPG. A multidisciplinary team of VA and DoD professionals (see Guideline Development Team) with experience in evaluating and managing active duty Service members and Veterans with schizophrenia comprised the Work Group, which, based on the evidence and using the GRADE approach, developed the recommendations, discussion sections, algorithm, and other clinical elements of this CPG.

B. Components of this Guideline

This CPG provides clinical practice recommendations for the care of patients with schizophrenia (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, quick reference guide, and a patient summary, which can be found at https://www.healthquality.va.gov/index.asp.

C. Racial and Ethnic Demographic Terminology in this Guideline

Demographic terms referring to an individual's race or ethnicity (e.g., "Hispanic," "Latino/a," "Asian," "Native American," "Black,", "African American," "White,"

"Caucasian") can be ambiguously defined and understood, reflecting diverse geographies, histories, cultures, and experiences. In alignment with the recent Executive Order on Further Advancing Racial Equity and Support for Underserved Communities through the Federal Government,[a] the Work Group used terms, such as "Black" rather than "African American" and "White" rather than "Caucasian" to avoid presumptions about ancestry and to promote inclusivity, clarity, and consistency. However, in order to represent accurately the evidence upon which this CPG is based, the Work Group generally deferred to racial and ethnic terminology as reported in the published systematic reviews, clinical trials, and other studies comprising that evidence when summarizing or otherwise referring to those studies. Consequently, usage of demographic terms in this CPG may appear inconsistent.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Ira Katz, MD, PhD, and Sandra Resnick, PhD, from VA; and LTC Shannon C. Ford, MD, FAPA, and Fuad Issa, MD, FAPA, from DoD.

The Work Group comprised individuals with the following areas of expertise: psychiatry, psychology, internal medicine, nursing, primary care, pharmacy, mental health counseling, and social work. Table 1 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with

- Determining the scope of the CPG;
- Crafting clinically relevant key questions (KQ) to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting, was contracted by VA to help develop this CPG.

[a] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government | The White House

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Ira Katz, MD, PhD (Champion)**
	Sandra Resnick, PhD (Champion)
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	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
Department of Defense	**LTC Shannon C. Ford, MD, FAPA (Champion)**
	Fuad Issa, MD, FAPA (Champion)
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	Annie Zhang, BA
	Andrea Dressel, BS
ECRI	James Reston, PhD, MPH
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Organization	Names*
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	Kate Johnson, BA
	Rachel Piccolino, BA
	Richa Ruwala, BA

*Additional contributor contact information is available in Appendix H.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(48) 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, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(49) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the 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 (see Determining Recommendation Strength and Direction).(50)

1. Confidence in the quality of the evidence
2. Balance of desirable and undesirable outcomes
3. Patient values and preferences
4. Other considerations, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

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.(51) 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).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice although it is unsupported by clinical evidence and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about an intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 2.

Table 2. 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 . . .

That a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence based and still important to clinical care) is important to note. The strength of each recommendation is shown in Recommendations.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., randomized controlled trials [RCT]) are typically supported by lower quality evidence and, in turn, *Weak*

recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(52, 53) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(54) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(55)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(56, 57) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2023 CPG recommendation categories can be found in Recommendations.

Table 3. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not Reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012)(56) and Garcia et al. (2014)(57)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(48) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care)(58) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(48) The disclosure form inquires regarding relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica). No COIs were identified among the CPG Work Group or the guideline development team.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(52, 59) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on September 8, 2021. The focus group aimed to gain insights into patients with schizophrenia of potential relevance and incorporate these insights into the CPG, as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and impacts of their care on their lives.

The patient focus group comprised a convenience sample of one person, a male Veteran in the VA health care system. The Work Group acknowledges this convenience sample is not representative of all patients with schizophrenia within the VA and DoD health care systems and, thus, findings are ungeneralizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix B. The patient focus group participant was provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with schizophrenia. The Work Group submits suggested performance metrics for VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. 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 sex, culture, ethnicity, and other differences.

B. 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.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to managing schizophrenia. Many Veterans, Service members, and their families have one or more co-occurring conditions. Because schizophrenia is sometimes accompanied by co-occurring conditions, managing schizophrenia collaboratively with other care providers is often best. Some co-occurring conditions might require early specialist consultation to determine necessary changes in treatment or to establish a common understanding of how care will be coordinated. This approach might entail reference to other VA/DoD CPGs (e.g., for Suicide Risk, SUD, Opioids, Major Depressive Disorder).[b]

VIII. Algorithm

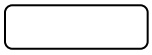
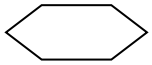
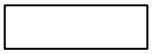
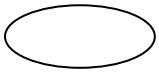
This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in managing patients with FEP or schizophrenia. This algorithm format represents a simplified flow of the management of patients with schizophrenia and helps foster efficient decision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

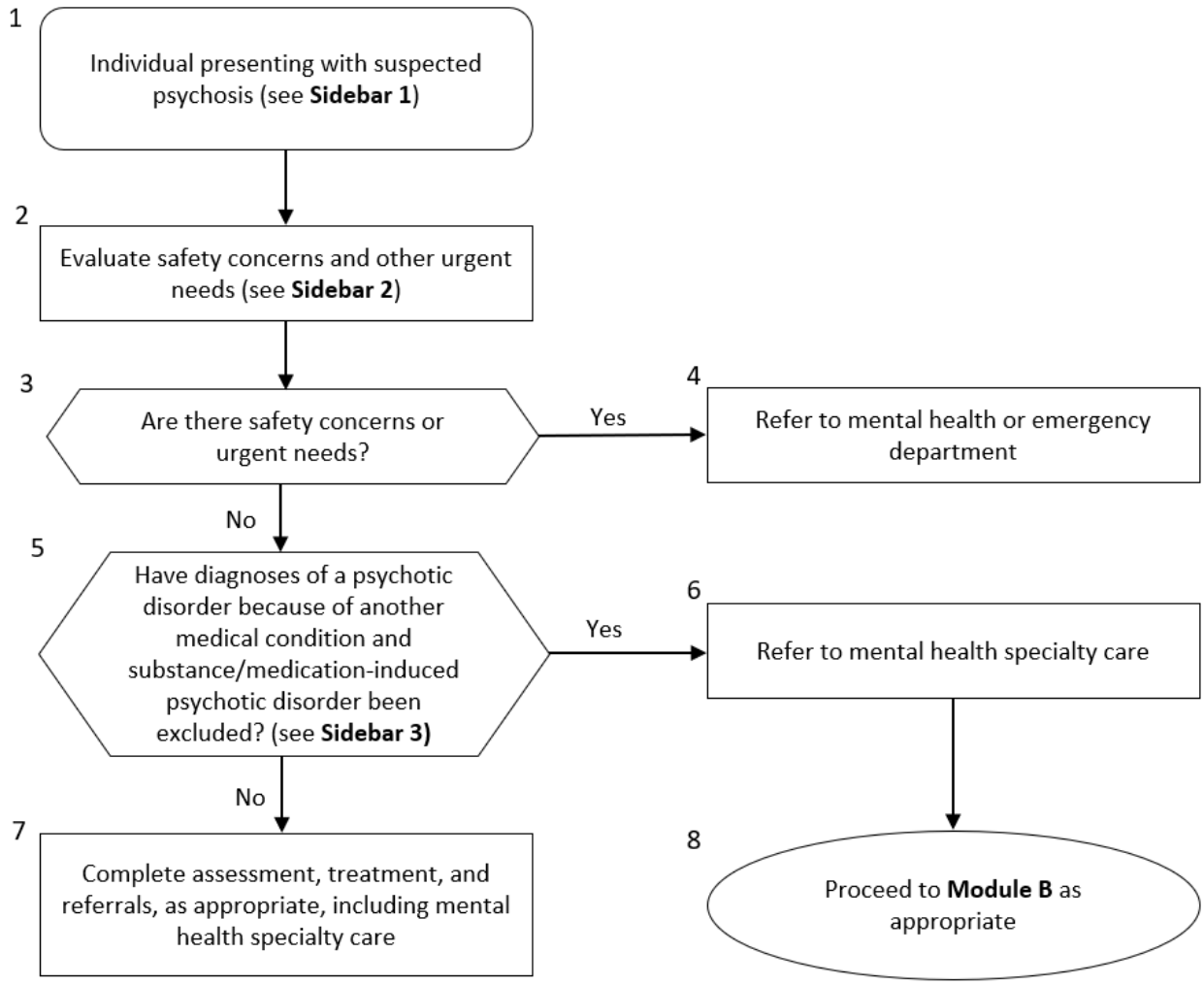
[b] The VA/DoD Clinical Practice Guidelines are available at: https://www.healthquality.va.gov/

be followed.(64) Sidebars 1–7 provide more detailed information to assist in defining and interpreting elements in the boxes.

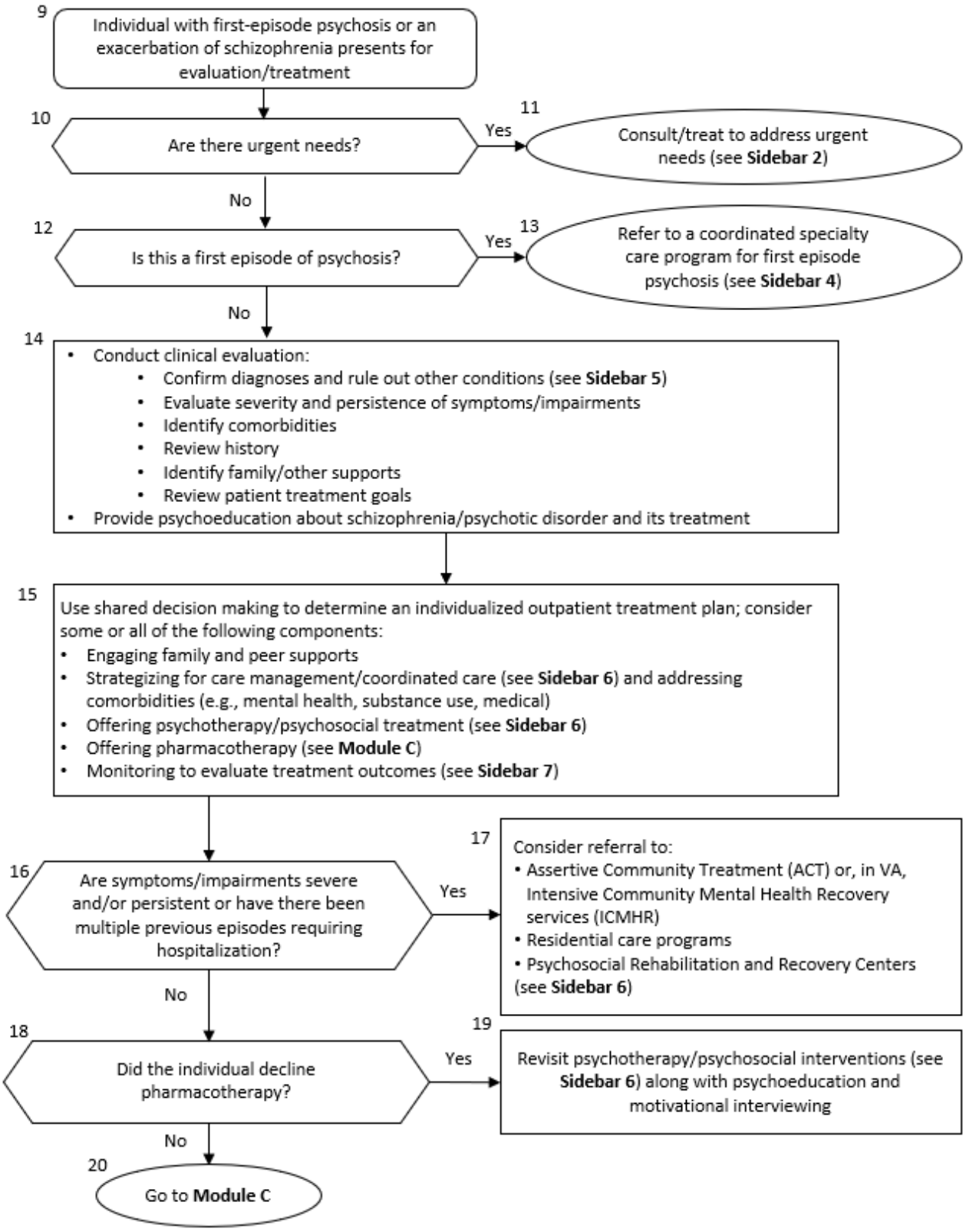
Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered “Yes” or “No.”
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within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

Appendix J contains alternative text descriptions of the algorithms.

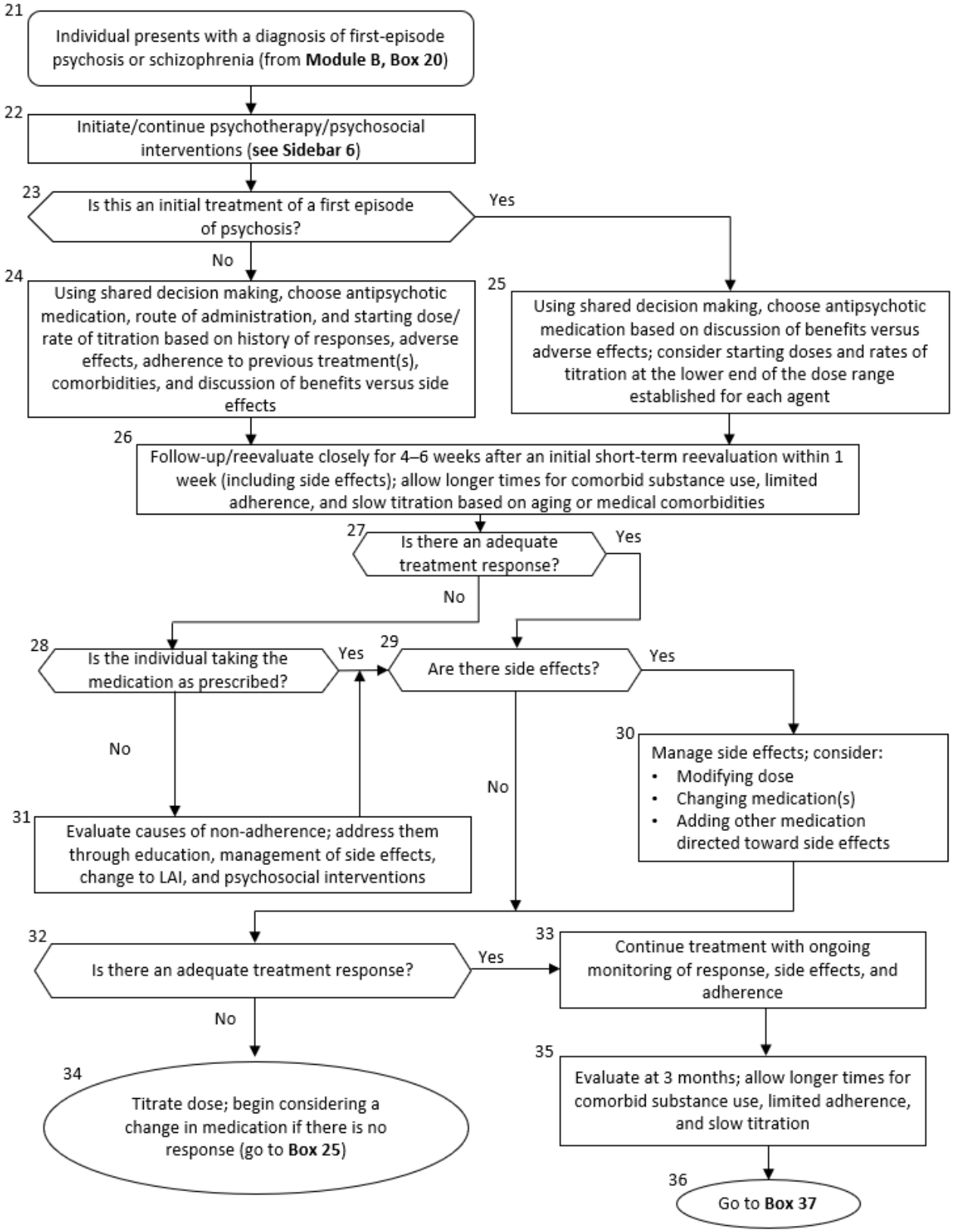
Module A: Primary Care Evaluation and Management of Suspected Psychosis or Possible Schizophrenia

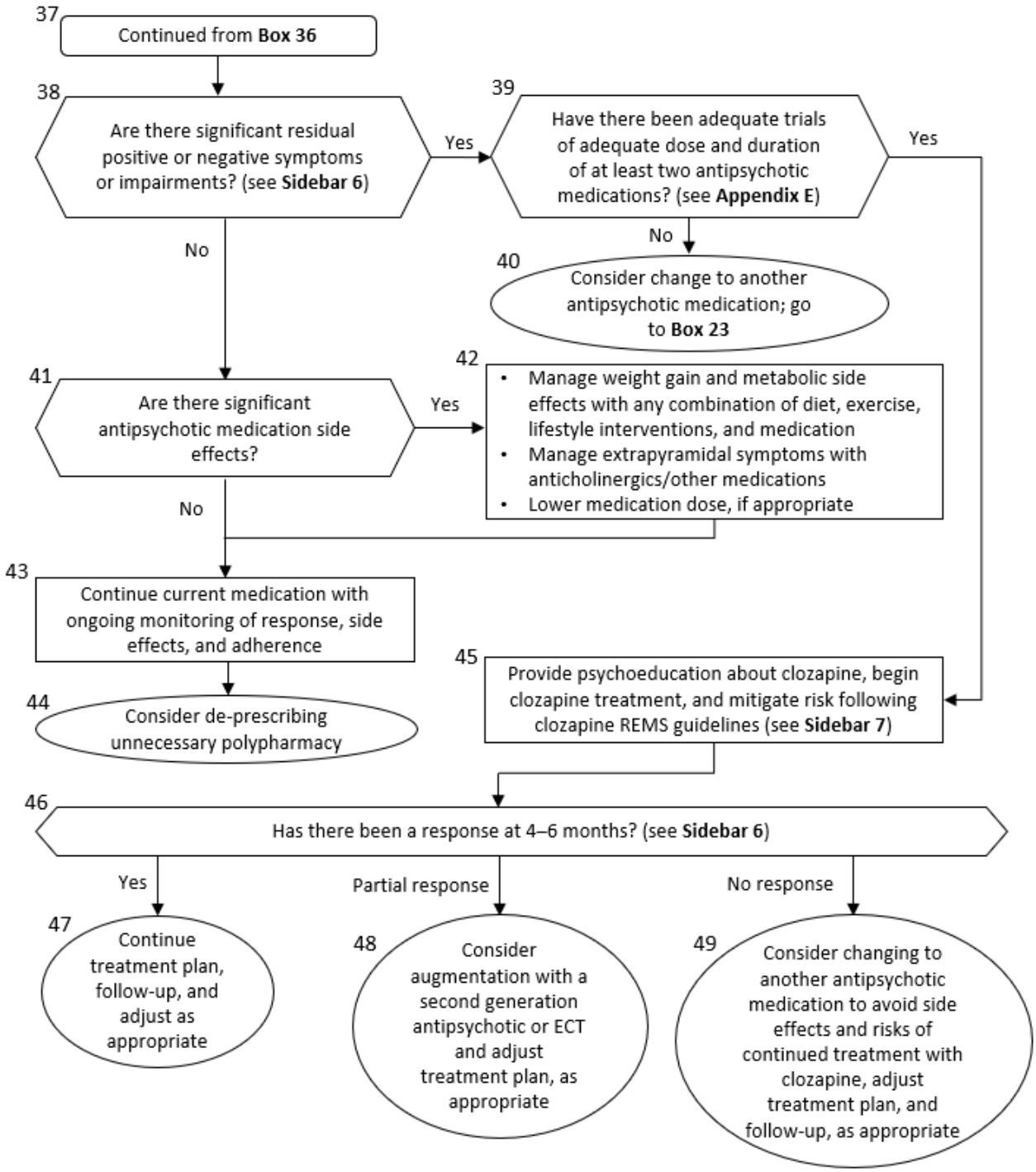


Module B: Evaluation and Management of First-Episode Psychosis and Schizophrenia by Mental Health Providers



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 (65)

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 (65)

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 (66)

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

IX. Recommendations

The evidence-based clinical practice recommendations listed (see Table 4) were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). 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 4. 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
	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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (cont.)	*Pharmacologic Interventions for Psychosis (cont.)*	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
	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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (cont.)	*Non-pharmacologic Interventions (cont.)*	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 cognitive training programs for the treatment of cognitive impairment and negative symptoms 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 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
		33.	We suggest the following psychotherapies and psychotherapeutic interventions in combination with pharmacotherapy for individuals with schizophrenia: • Cognitive behavioral therapy for psychosis • Acceptance and mindfulness-based therapies, • Metacognitive therapy, or • Positive psychology interventions.	Weak for	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of First-Episode Psychosis and Schizophrenia (cont.)	*Non-pharmacologic Interventions (cont.)*	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] For additional information, see Determining Recommendation Strength and Direction.
[b] For additional information, see Recommendation Categorization.

A. Assessment and Evaluation

a. Suspected Psychosis

Recommendation

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)

Discussion

Evidence was limited for the use of screening or assessment instruments to identify or predict whether an individual who presents for care will transition to psychosis. The Work Group reviewed evidence from three SRs and four cohort studies that evaluated

the prognostic (indicating or predicting potential evolution of presenting symptoms to psychotic disorder) or diagnostic (identifying a specific disorder) utility of several screening tools to identify psychosis, including a risk calculator tool.(67-73) None of the reviewed studies addressed the use of the Prevention through Risk Identification, Management, and Education (PRIME) screening tool or the Mini International Neuropsychiatric Interview (MINI) (two screening instruments frequently used in the field) because no studies using these tools met inclusion criteria for the systematic evidence review.

One SR of six prognostic studies analyzed the prognostic accuracy of the Comprehensive Assessment of At-Risk Mental States (CAARMS).(67) The SR found acceptable prognostic accuracy of CAARMS but poor specificity (the ability of the instrument to correctly identify individuals without the psychotic disorder).(67) Another SR contained a meta-regression of six CAARMS studies compared with five Structured Interview for Psychosis-Risk Syndromes (SIPS) studies and found significantly higher sensitivity (the ability of the instrument to correctly identify individuals with a psychotic disorder) for the SIPS compared with the CAARMS ($p<0.001$), with no difference in specificity.(67, 68) One prognostic cohort study, which compared the DSM-5-Attenuated-Psychosis-Syndrome (DSM-5-APS) criteria with the CAARMS, showed acceptable prognostic accuracy at a mean follow-up of 1.5 years for the DSM-5-APS, similar to the CAARMS.(69) The discriminative performance of the Early Psychosis Screener-26 (EPS-26) was evaluated for concurrent validity against the SIPS by one diagnostic cohort study.(70) It reported that the diagnostic accuracy of the EPS-26 was excellent when distinguishing individuals at clinically high risk (CHR) versus those at clinically low risk (CLR) for psychosis but low when distinguishing individuals at CHR for psychosis versus patients with FEP.(70) One SR of 14 diagnostic accuracy studies generally found that the Prodromal Questionnaire (PQ) accurately predicted psychosis for individuals defined by investigators as ultra-high risk (UHR) for progression to psychosis and reported that various versions of the PQ (PQ-92, PQ-16, and PQ-B) were accurate diagnostic predictors.(71) One diagnostic cohort study using the CAARMS as a reference test found that the Italian version of the PQ-6 (iPQ-6) was acceptable for the detection of individuals who appear to be UHR for psychosis, with one-year follow-up, but not sensitive enough to distinguish between UHR and psychosis.(72) The SIPS was evaluated by one SR consisting of five prognostic accuracy studies of individuals within two years of screening as part of a meta-analysis of several different psychometric interviews used to determine referrals to high-risk care and found excellent sensitivity but poor specificity.(68) Finally, the Work Group considered findings from one prognostic cohort study designed to validate a previous North American Prodrome Longitudinal 2 (NAPLS-2) study (73) and concluded that the model appears to predict psychosis with a balanced accuracy (BAC) of 68% (sensitivity: 68%; specificity: 63%) in the PRONIA/UHR cohort and 70% (sensitivity: 73%; specificity: 66%) in individuals with CHR/ROD. However, the NAPLS-2 risk calculator did not show improved BAC compared with CAARMS or SIPS BAC.

Evidence suggests that the use of evidence-based screening or assessment tools in the specialty mental health care setting is potentially beneficial for individuals with suspected psychosis. However, the potential benefits of using identified screening or assessment tools slightly outweighed the potential harms of not using those identified tools. Although results using screening or assessment tools alone are insufficient to establish a diagnosis, when used in conjunction with clinical evaluations they appear to assist specialty mental health providers in identifying individuals who might have early symptoms of psychosis or might develop symptoms of psychosis in the future.

Overall, most of the screening and assessment tools examined in the evidence base had at least acceptable accuracy for predicting transition to psychosis but showed low specificity. This finding reveals a weakness in the body of the literature because no gold standard test exists that provides both high sensitivity and high specificity to differentiate psychosis from other mental health conditions or to predict the risk of psychosis onset. The use of different reference standards for screening or assessment instruments in each study also limits cross-study inferences about the acceptability of one specific instrument.(70) The strength of the evidence was low for most of the instruments assessed, except the SIPS, which was determined to be of moderate strength. However, most studies evaluated instruments that were used with populations already identified as at a clinically high risk of developing psychosis.

Although the patient focus group did not address the diagnosis or screening processes or instruments in the VA or DoD health care systems, the Work Group noted that in DoD a suspected psychosis diagnosis is potentially career ending for some individuals and might be a barrier to individual acceptance of routine or indicated screening practice. For others, obtaining an accurate diagnosis is desired. Also, inherent provider biases might occur in determining which patients meet indications for psychosis screening, and, if biases exist, they might present equity issues. Finally, some screening or assessment tools were not developed for or intended to be used by primary care physicians in a primary care clinical setting; they were developed and validated to be used by specialty mental health providers for use in a specialty care clinic to aid in diagnosis and prognosis determinations. The process of determining diagnosis and prognosis is multifactorial and includes the expertise and clinical formulation of the specialty care provider; screening and assessment provide data points to help with a comprehensive formulation.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(67–73) The confidence in the quality of the evidence was low. The benefits of using identified screening or assessment tools to screen individuals in specialty care clinics for suspected psychosis slightly outweighed the potential harms. Individual values and preferences varied somewhat because a stigma is attached to the diagnosis of psychosis for most individuals. Overall, the SIPS appeared to be the most robust tool of the instruments included in the review. It was found to be useful as a screening tool but not as a

diagnostic tool because of its high sensitivity and low sensitivity. The body of evidence had some limitations, including a paucity of published studies. Most studies evaluated instruments, tools, or both in populations at high risk of psychosis using an accurate but imperfect reference test, lacked clarity regarding the independent interpretation of reference and index tests, or both. Problems also arose with the validity of findings across studies. The degree of accuracy when comparing a specific psychosis screening or assessment instrument with various other instruments is imprecise because no accepted gold standard psychosis screening or assessment instrument exists to aid with valid comparisons across studies. Thus, the Work Group made the following recommendation: For individuals with suspected psychosis, we suggest using evidence-based screening tools in specialty mental health settings to differentiate or identify individuals, or both at risk for transition to psychosis.

Recommendation

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)

Discussion

Three prognostic cohort studies evaluated the diagnostic and prognostic utility of magnetic resonance imaging (MRI)-based predictor models or biomarker panels to diagnose, identify, or provide a prognostic risk of transition to psychosis.(73-75) No studies that met inclusion criteria for the evidence review showed evidence to support pharmacogenomics testing.

In a prognostic cohort study conducted in Germany and Switzerland, MRI accuracy in predicting transition to psychosis within a mean 4.3-year follow-up was determined to have a BAC of 80.4% (sensitivity: 75.8%; specificity: 85%; false positive rate: 14%).(73) The study sample consisted of patients who were already defined as high risk for psychosis using the Brief Psychiatric Rating Scale (BPRS) or the Scale for the Assessment of Negative Symptoms (SANS). Another prognostic cohort study evaluated whether levels of circulating molecular lipids have any relationship to adverse clinical outcomes in individuals identified as CHR for psychosis.(74) Finally, the Work Group reviewed evidence from one prognostic cohort study that prospectively and retrospectively examined the use of a serum biomarker panel to identify first-onset psychosis patients at risk for developing schizophrenia.(75)

Although the MRI-based prediction system appeared reasonably accurate, the study population inclusion criteria were narrow. Moreover, challenges exist with logistic system implementation requirements mandating the use of specifically trained interviewers because they would be required to integrate clinical expertise with the use of a machine learning algorithm involving constructed sets of predictive

neuroanatomical features derived from high-dimensional maps. This challenge would potentially limit the feasibility and availability of MRI-based risk prognostic tools across less specialized mental health services. Although serum biomarker panels also demonstrated good-to-excellent accuracy in different cohorts and blood tests and although using such panels in conjunction with structured interviews has the potential to enhance the ability of providers to predict transition to psychosis, more research is needed before further recommendations can be developed.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(73–75) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a small number of studies that met inclusion criteria, a lack of SRs, a small sample size for one of the studies, and serious imprecision. The benefits of using MRI or serum biomarker panels to predict psychosis onset or make diagnoses are balanced with the potential harms of using these tools. Although the patient focus group did not address the use of screening tool preferences, patient values and preferences vary. Many patients prefer noninvasive tests, and some might oppose the determination of diagnosis via serum or imaging because of the potential negative career impact; yet others might welcome a diagnosis. Finally, this assessment strategy has both cost and feasibility challenges because many DoD and VA clinics have limited MRI access. Even though reviewed study results appear promising, more research is needed to determine more precisely the accuracy and feasibility of using biomarkers and MRI-based prediction systems to differentiate psychosis from other mental health disorders or to predict the risk of onset. Thus, the Work Group made the following recommendation: 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.

B. Management of First-Episode Psychosis and Schizophrenia

a. First-Episode Psychosis

Recommendation

3. We recommend treatment/management with early intervention services for individuals with first-episode psychosis.
   (Strong for | Reviewed, New-added)

Discussion

Evidence for using early intervention services (EIS) in the treatment and management of individuals with FEP was identified in one SR with 10 RCTs (76) and an additional RCT.(77) In both cases, EIS were compared with treatment as usual (TAU) or standard care. Both found that EIS improved global functioning and involvement in school or worked better than TAU at 9–24 months in individuals with FEP or early-phase schizophrenia spectrum disorders.(76, 77) Additionally, the studies found that EIS

improved total symptom severity, positive symptom severity, negative symptom severity, general symptom severity, and remission more than TAU at 9–24 months in individuals with FEP or early-phase schizophrenia spectrum disorders.(76, 77)

Addington et al. (2013; included in the Correll et al. [2018] SR) initially defined 32 evidence-based components of FEP services, which became the foundation for EIS.(76) In the studies discussed above, EIS were defined as "specifically designed for the needs of people with early-phase psychosis and consisting of a multimodal treatment program, including several psychosocial and psychopharmacologic interventions (e.g., case management, psychotherapy, supported employment and education, and family support) that are provided from one team in a coordinated, integrated fashion."

Eisen et al. (2022; not included in the evidence base nor impacting the strength of the recommendation) states that in the U.S., "the recognition of the link between duration of untreated psychosis and patient outcomes has led to the establishment of early intervention in psychosis services. These services are termed Coordinated Specialty Care (CSC), which includes a range of evidence-based interventions offered within a recovery-oriented and shared decision-making framework."(78)

The National Institutes of Health defines CSC as "a general term used to describe a certain type of treatment for FEP. Many different programs are considered CSC. Some examples of CSC programs in the U.S. include (but are not limited to) NAVIGATE, The Connection Program, OnTrackNY, Specialized Treatment Early in Psychosis (STEP) program, and Early Assessment and Support Alliance (EASA)."(79)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(76, 77) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations in that they did not measure which component or components are key to EIS's effectiveness, nor did they measure the duration of that effectiveness. Additionally, a cost-benefit analysis of the effectiveness would be valuable. The benefits of treatment, management, or both with EIS for individuals with FEP (e.g., improvement in total symptom severity) outweighed the minimal burdens outlined in the evidence review. Patient values and preferences varied because individuals and their families have different preferences for their treatment plan. Thus, the Work Group made the following recommendation: We recommend treatment/management with early intervention services for individuals with first-episode psychosis.

Recommendation

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)

Discussion

An SR and meta-analysis of RCTs, by Camacho-Gomez et al. (2020), was performed comparing family intervention for psychosis (FIp) to TAU or TAU plus other psychosocial interventions.(80) Evidence suggests that FIp was favorable for relapse reduction, fewer days hospitalized, less severe psychotic symptoms, and improved functionality when compared with TAU, other psychosocial interventions, or both. Regarding relapse reduction, a meta-analysis of six RCTs showed a significant reduction in relapse favoring FIp up to 24 months of follow-up. A subgroup analysis showed a significant relapse reduction rate for FIp compared with TAU. Duration of hospitalization was also reviewed, and the evidence showed a significant reduction in length-of-stay with the use of FIp compared with TAU at 24 months of follow-up. Six comparisons of individuals with FEP treated with the FIp intervention compared with TAU found a significant reduction in psychotic symptoms and significant reduction of 3.31 hospital readmission days at 24 months of follow-up, with substantial heterogeneity. When compared with other active interventions, a reduction of 4.57 days in favor of FIp was observed, indicating an absence of heterogeneity Also, statistically significantly improved functionality occurred compared with TAU at follow-up.

Chien et al. (2020) conducted an RCT that aimed to assess the effects of a five-month family-facilitated problem solving–based self-learning program (PBSP) plus TAU versus a family psychoeducation group (FPGP) plus TAU versus TAU alone.(81) Participants in the study included family members of Chinese adults who were diagnosed with a psychotic disorder, according to the DSM-IV-TR or DSM-5, with recent onset of symptoms (fewer than five years at the time of recruitment). Participants were age 18–60 and spoke Cantonese or Mandarin. Findings suggested that PBSP plus TAU led to a greater, more significant reduction in caregiver burden, symptoms, and hospitalizations compared with FPGP plus TAU and TAU alone.

According to Mueser et al. (2013), SUDs are common in people with psychotic disorders and other serious mental illness (SMI).(82) Mueser et al. (2013) conducted an RCT for individuals with a comorbid SUD comparing a short-term (2–3 months) brief family education (ED) program to a longer-term (9–18 months) program known as a family intervention for dual disorders (FIDD), which combined education with teaching communication and problem-solving skills.(82) Participants were randomized to either ED or FIDD and assessed at baseline and every six months for three years. Evidence suggests that FIDD increases the benefits of substance use treatment, reduces alcohol and nonprescribed drug use severity, and improves symptoms compared with ED. Regarding family outcomes, no difference was found in the physical component between interventions or family experience interview schedule benefits; however, FIDD improved the mental component.

Camacho-Gomez et al. (2020) suggested that FIp was effective at decreasing relapses in individuals with FEP, consistent with the effects observed in other individuals with schizophrenia.(80) Evidence suggests that actively involving the relatives of individuals

with both recent psychosis onset and schizophrenia contributes considerably toward reducing relapse risk. Moreover, FIp might help relatives increase their understanding of this disorder and its impact on personal, social, and interpersonal functioning; identify exacerbated psychotic symptoms; acquire problem-solving techniques during acute episodes; and obtain awareness of the importance of treatment adherence.

Evidence suggests that the caregiver-facilitated PBSP in early-stage psychosis can be effective in enhancing psychosocial health for the individual (e.g., related to symptom severity and recovery) and for the family, the caregiver, or both (e.g., related to burden and problem solving). According to Chien et al. (2020), the findings also support the use of PBSP as a family-oriented intervention during early psychosis in community-based mental health services when therapists and resources are limited and a psychiatric nurse can serve in the role of resource person.(81)

Other evidence from Mueser et al. (2013) suggests that participants with dual diagnoses who were randomized to either the FIDD or the brief ED programs demonstrated significant improvements across a range of outcomes over the three-year study.(82) Participants in both programs showed improvement in substance use, overall psychiatric symptoms, stable days in the community, and global functioning.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(80–82) The Work Group's confidence in the quality of evidence was moderate. Patient values and preferences varied because some individuals might prefer less family involvement in their treatment. Thus, the Work Group made the following recommendation: We recommend the use of family interventions (including problem solving–based self-learning, education, and mutual family support) for individuals with first-episode psychosis.

Recommendation

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)

Discussion

Bond et al. (2014; not included in the evidence base nor impacting the strength of the recommendation) defines Individual Placement and Support (IPS) as a model of supported employment designed to help individuals gain and maintain competitive employment.(83) Findings from the systematic evidence review suggest that IPS provides more benefits for individuals with FEP compared with TAU. Three studies examined critical employment outcomes up to a six-month follow-up.(84-86) A study by Nuechterlein et al. (2020), which looked at IPS augmented with workplace fundamentals skills training compared with TAU, favored IPS and workplace fundamentals skills training on rates of competitive employment or engagement in school.(84) Allott et al.

(2013) also found that IPS was superior to TAU on a combined measure of employment and school engagement.(85) Killackey et al. (2019) showed advantages of IPS over TAU for employment status but not educational status.(86)

At timeframes greater than six months, IPS was favored over TAU on measures of employment status and days worked in a study by Erickson et al. (2021).(87) Nuechterlein et al. (2020) favored IPS on a combined measure of employment and engagement in school.(84) It also found a difference in treatment adherence at six months favoring IPS and workplace fundamentals over TAU.(84) In Killackey et al. (2019), the benefits of IPS on employment status were no longer observed after six months, and there continued to be no benefit in educational status.(86)

That this recommendation evaluates the evidence for IPS as a single intervention is important to note, but models of CSC for individuals with FEP include supported employment and supported education as an important component of care (see Recommendation 3).

Patient preferences vary regarding IPS because participation is predicated on an individual's interest in obtaining a competitive job. According to Bond et al. (2014; not included in the evidence base nor impacting the strength of the recommendation), approximately 65% of individuals with significant psychiatric disabilities wish to be employed, but only 15% are employed.(83) The provision of IPS is consistent with the results of this CPG's patient focus group in which a primary theme was that "goals should encompass foundational elements of being able to live, work and learn" (see Appendix F).

Overall, IPS is an intensive support model designed to be integrated into mental health treatment that requires a trained workforce able to work with individuals with psychiatric disabilities and with employers in community businesses. The "place then train" model of IPS can differ from how vocational rehabilitation specialists are traditionally educated and trained. The need for a high level of service intensity, a strong interdisciplinary team approach, and a community-based service delivery model means that implementing IPS with fidelity and maintaining high levels of fidelity over time can be challenging. Although not included in the evidence base, strategies to support implementation exist, but they can be resource intensive.(88)

IPS is required in VA by VHA Directive 1163[d] but is currently unavailable in DoD. Active duty Service members experiencing psychosis without a separation date receive a salary from DoD, and, thus, participation in employment, education, or both is infeasible under current rules. For example, an existing skill bridge program allows for active duty Service members on terminal leave to participate in unpaid internships, but it is not designed for individuals experiencing FEP. However, given the logistical and regulatory

[d] Available at: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=8438

challenges, currently no research examining the feasibility and effectiveness of IPS exists in DoD individually or as part of a coordinated VA and DoD FEP program.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(84–87) The Work Group's confidence in the quality of the evidence was low. Although confidence in the quality of the evidence at six-months follow-up was moderate, the quality of the evidence for longer timeframes was low.(84-86) At the six-month point, some inconsistency occurred among studies on educational outcomes, with two studies showing benefits and one failing to demonstrate such a difference (84, 86, 87). The benefits of IPS (e.g., improvement in employment outcomes) outweighed the potential harms because no adverse events of participation in IPS have been noted in the evidence base. Patient values and preferences vary somewhat, given that employment might not be a goal of every individual with schizophrenia. Additionally, although VA benefits and entitlements are protected for Veterans in a VHA IPS program, paid employment might negatively impact entitlements outside the VA setting, such as supplemental security income. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

Specialized early intervention services (EIS) are multidisciplinary, community-based mental health teams that provide a range of treatments (see Recommendation 3) delivered through an assertive outreach model of care. Care coordinators have restricted caseload sizes, which allows them to work more intensively with individuals and engage them in treatment.(89) Treatment services are usually limited to two years, and individuals are typically discharged to specific providers or to an adult community mental health team.(89) Extended specialized EIS prolong the duration of specialized EIS up to a maximum of five years.

Limited evidence indicates that extended specialized EIS might improve global psychotic symptoms (i.e., positive, negative, and mood symptoms) and engagement in services.(89) The evidence base included two SRs and four RCTs comparing extended specialized EIS with TAU non-protocoled care. Some evidence exists of benefit for symptom outcomes and disengagement but no demonstrated effect on overall functioning (either educational or social), employment status, remission, or psychiatric hospital admissions.(89, 90) Though the body of supporting evidence was small, the benefits of specialized EIS slightly outweighed the harms and burdens. No evidence

supported any one component of extended EIS being most beneficial nor any specific time of services rendered. Thus, the Work Group could not make a recommendation for or against a specific duration of treatment.

Patient preferences vary regarding this treatment. Because of the time intensive nature of this intervention, some individuals and their families might not prefer the added burden of frequent visits. Further, the intervention itself would require many qualified workers with focused training—resources that might be unavailable in some locations or to some patient populations.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(89, 90) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small study samples, poor blinding procedures, unconcealed allocation, and high attrition in control groups. The benefits of extended specialized early intervention in FEP (e.g., improved outcomes in global psychotic symptoms and disengagement) slightly outweighed the potential burdens related to resource use, equity, and feasibility. Individual values and preferences varied somewhat because some individuals prefer fewer intensive interventions. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

The systematic review of the evidence related to the treatment of FEP yielded one SR of 17 RCTs (n=3,156).(91) The study was limited by design to only 16 weeks of treatment. With this limitation, the study lacked sufficient evidence to make a treatment recommendation of a specific timeframe. Zhu et al. (2017) also reviewed treatment of acute psychosis.

The patient focus group provided no input regarding the treatment of individuals with FEP. However, the patient focus group did note that medications were generally helpful throughout the experience of psychosis.

Further areas of research include study beyond 16 weeks of second-generation antipsychotics and research into maintenance treatment strategies for individuals with first episode psychosis.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(91) The available evidence did not provide information about the length of treatment required to maximize responses or to minimize the rate of relapses. The benefits (e.g., preventing relapse) of a specific duration for treatment with an antipsychotic were balanced with harms (e.g., side effects associated with medication not having an impact). Patient values and preferences were somewhat varied. Thus, the Work Group made the following recommendation: 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.

b. Pharmacologic Interventions for Psychosis

Recommendation

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)

Discussion

Evidence supports the use of antipsychotic medications (other than clozapine) as a class for the treatment of an acute episode of schizophrenia. The evidence base included three individual RCTs (92-94) and multiple SRs and meta-analyses (91, 95-106) examining the efficacy of antipsychotic medications for the treatment of acute symptomatology in either the first episode of schizophrenia or in repeat acute episodes. In the largest SR and meta-analysis, which included 167 double-blind RCTs (n=28,102), Leucht et al. (2017) reported that 51% of people treated with an antipsychotic medication had at least a minimal response versus 30% in the placebo groups.(107)

This recommendation is based on several considerations. First, the recommendation for antipsychotic medications as a class is based on commonalities in their mechanisms of action.(107) They exert their therapeutic effect through the modulation of the dopamine system; most of the currently approved antipsychotics are dopamine D2 receptor antagonists. In addition, antipsychotic medications share similar efficacy (with the exception of clozapine, which is reserved primarily for the treatment of people who either failed to adequately respond to other antipsychotic medications or for the treatment of suicidality).(108) Therefore, the Work Group considered antipsychotic medications as a class rather than individually when formulating the recommendation. Second, the GRADE rating for the quality of the studies was largely based on the Leucht et al. (2017) meta-analysis (107) because this assessment of antipsychotic efficacy was the most comprehensive, included most of the other studies in the

evidence database, and, consistent with the Work Group decision, considered antipsychotic medications as a class. Although a large percentage of the 167 studies analyzed in Leucht et al. (2017) have serious flaws and poor reporting, some are of good quality.(107) However, because the risk factor analysis found that none of the standard risk of bias factors was a significant moderator of treatment effect (meaning the effect size was consistent across good, fair, and poor-quality studies), and the analysis also adjusted for publication bias (107), the overall GRADE rating for the quality of the studies was judged to be moderate for this evidence base. Third, the benefits of antipsychotic medication treatment strongly outweigh the potential harms and burdens associated with withholding antipsychotic medication. Specifically, there is a significant benefit of symptom reduction, which is associated with reduced patient distress and increased receptivity for psychosocial and recovery-oriented treatments. The potential harms of not providing these medications include increased risk of self-harm or harm to others; impaired work or social functioning or both; decreased QoL; distress from untreated symptoms; and family burden. Significant harms are associated with antipsychotic medication treatment, including cardiovascular, metabolic, and motor side effects; sedation; and others. However, the potential benefits of treatment far outweigh the potential harms associated with withholding treatment or with the use of antipsychotic medications.

Leucht et al. (2017) found that antipsychotic medications differ from each other in their side effect profile, which reflects their varied actions at the various neurotransmitter systems.(107) First-generation antipsychotics (FGA) (e.g., fluphenazine, haloperidol) are more prone to produce persistent extrapyramidal symptoms (EPS), including pseudoparkinsonian symptoms, akathisia, dystonias, tardive dyskinesia (TD), and neuroleptic malignant syndrome, especially when used at higher doses. In contrast, second-generation antipsychotic medications (SGA) (e.g., olanzapine, quetiapine, risperidone) are less likely than FGAs to cause EPS but might be associated with increased risk of weight gain and other metabolic abnormalities, including hyperlipidemias and type 2 diabetes mellitus. FGAs and SGAs that bind strongly to the dopamine D2 receptor might also cause prolactin elevation, which can lead to galactorrhea, dysmenorrhea, and sexual dysfunction. Finally, both FGAs and SGAs might cause cardiovascular side effects, including dysrhythmias and QT prolongation, and, rarely, seizures. Considering the variability in the side effect profile across the different antipsychotic medications, the choice of antipsychotic medication should be based on an individualized evaluation that considers patient specific characteristics and preferences and the side effect profiles of the medications.

Patient preferences vary regarding the use of antipsychotic medications. For example, individuals with schizophrenia might have concerns about experiencing one or more of the side effects associated with a particular antipsychotic agent. They might also experience the need for long-term treatment to be a burden, both practical and psychological. Finally, patient preferences might fluctuate secondary to changes in their

insight into the need for medications. Also to consider are equity, acceptability, and subgroups. The equity issues revolve around the decreased use of SGAs in African American populations, which exposes African American patients to increased risk of EPS, including TD, and possibly adversely impacts adherence and treatment response. The acceptability issues are related to the side effects associated with antipsychotic medications. Subgroup considerations include the use of a lower antipsychotic dose in people who are experiencing FEP and the need for lower doses in older adults with schizophrenia because of reduced rates of drug metabolism.(108)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(91-107) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including a marked risk of study bias. However, the risk factor analysis found that none of the standard risk of bias factors was a significant moderator of treatment effect (meaning the effect size was consistent across good, fair, and poor-quality studies).(107) The benefits of antipsychotic medications for the treatment of an acute episode of schizophrenia (e.g., symptom reduction, which is associated with reduced patient distress and increased availability for complementary non-pharmacologic treatments, such as supported employment) and the potential harms of not providing these medications (e.g., increased risk of self-harm or harm to others; impaired work or social functioning or both; decreased QoL; distress from untreated symptoms; and family burden) outweighed the potential harm of adverse events (e.g., cardiovascular, metabolic, and motor side effects; sedation; and others). Patient values and preferences varied because some individuals with schizophrenia might have concerns about experiencing one or more of the side effects associated with a particular antipsychotic agent. Finally, patient preferences might fluctuate secondary to changes in their insight into the need for medications. Some individuals might also perceive the need for long-term treatment to be a burden, both practical and psychological. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

A large evidence base supports the use of antipsychotic medication as a class for maintenance treatment of schizophrenia to prevent relapse and hospitalization. The evidence base comprises multiple SRs (95-98, 107, 109-111) and individual RCTs (112-114) (95-98, 109-111) that examined the efficacy of antipsychotic medications for maintenance treatment. In an SR and meta-analysis of 75 RCTs (n=9,145), Ceraso et al. (2020) reported that antipsychotic medications were more effective than placebo for preventing relapse (24% versus 61%; RR: 0.38, 95% confidence interval [CI]: 0.32–0.45) and hospitalization (7% versus 18%; RR: 0.43, 95% CI: 0.32–0.57). (111)

This recommendation is based on several considerations. First, all antipsychotic medications exert their therapeutic effect through the modulation of the dopamine system; most of the currently approved antipsychotics are dopamine D2 receptor antagonists. Antipsychotic medications share similar efficacy (with the exception of clozapine, which is reserved primarily for the treatment of people who either failed to adequately respond to other antipsychotic medications or for the treatment of suicidality).(108) Therefore, the Work Group considered antipsychotic medications as a class, rather than considering each medication individually.

Although the confidence in the quality of the evidence for pairwise comparisons of antipsychotic medications ranged from very low to moderate, the grouping of all antipsychotic medications as a class led to the overall judgment of moderate confidence in the quality of the evidence. The overall judgment of moderate is further supported by the observation that considerable consistency exists across the studies, regardless of the GRADE of evidence for an individual study (i.e., even studies rated very low observed the same efficacy for antipsychotic medications as the studies rated moderate to high). Second, the benefits of antipsychotic medication treatment strongly outweigh the potential harms and burdens associated with withholding antipsychotic treatment. Specifically, preventing the worsening of symptoms is a significant benefit associated with decreased levels of distress and increased availability for psychosocial and rehabilitation- and recovery-oriented treatments (e.g., supported employment). The potential harms of withholding these medications include increased risk of self-harm or harm to others; impaired work or social functioning or both; decreased QoL; distress from untreated symptoms; engagement with the justice system; and family burden. In

contrast, the harms associated with antipsychotic medication treatment include cardiovascular, metabolic, and motor side effects; sedation; and others. In summary, the potential benefits of treatment and the harms associated with withholding treatment far outweigh the potential harms associated with the use of antipsychotic medications.

Ceraso et al. (2020) and Leucht et al. (2017) found that antipsychotic medications differ from each other in their side effect profile, which reflects their different actions at the various neurotransmitter systems.(107, 111) FGAs (e.g., fluphenazine, haloperidol) are more prone to produce extrapyramidal symptoms, including pseudoparkinsonian symptoms, akathisia, dystonias, TD, and neuroleptic malignant syndrome, especially when used at higher doses. In contrast, SGAs (e.g., olanzapine, quetiapine, risperidone) are less likely than FGAs to cause EPS but might be associated with an increased risk of weight gain and other metabolic abnormalities, including hyperlipidemias and type 2 diabetes mellitus. FGAs and SGAs that bind strongly to the dopamine D2 receptor might cause prolactin elevation, which can lead to galactorrhea, dysmenorrhea, and sexual dysfunction. Finally, both FGAs and SGAs might cause cardiovascular side effects, including dysrhythmias and QT prolongation, and, rarely, seizures. Considering the variability in the side effect profile across the different antipsychotic medications, the choice of antipsychotic medication should be based on an individualized evaluation that considers individual characteristics, including culturally influenced beliefs about mental illness and medication, and preferences and the side effect profiles of the different antipsychotic medications.

Patient preferences vary regarding the use of antipsychotic medications. For example, individuals with schizophrenia might have concerns about experiencing one or more of the side effects associated with a particular antipsychotic agent. They might also perceive the need for long-term treatment to be a burden, both practical and psychological. Also to consider are equity, acceptability, and subgroups. The equity issues revolve around the decreased use of SGAs in African American populations, which exposes African American individuals to increased risk of EPS, including TD, and possibly adversely impacts adherence and treatment response. The acceptability issues are related to the side effects associated with antipsychotic medications (see Recommendations 14–18 for the management considerations of individuals with marked antipsychotic medication side effects). Subgroup considerations include the use of lower antipsychotic doses in adolescents and elderly people with schizophrenia because of increased sensitivity and reduced rates of drug metabolism, respectively.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(95-98, 107, 109-114) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including a marked risk of bias. The benefits of antipsychotic medications for maintenance treatment of schizophrenia to prevent relapse and hospitalization (e.g., decreased relapse and hospitalization rates) and the potential harms of withholding these medications (e.g., increased risk of self-harm or harm to

others; impaired work or social functioning or both; decreased QoL; distress from untreated symptoms; engagement with the criminal justice system; family burden) outweighed the potential harm of adverse events (e.g., cardiovascular, metabolic and motor side effects; sedation). Patient values and preferences vary because some individuals with schizophrenia might have concerns about experiencing one or more of the side effects associated with a particular antipsychotic agent. Some patients might also perceive the need for long-term treatment to be a burden, both practical and psychological. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

Treatment with non-clozapine antipsychotic medications improves outcomes for symptoms, relapses, hospitalizations, and remissions in individuals with non-refractory schizophrenia. Antipsychotic medications have been found to be beneficial in individuals with schizophrenia, as demonstrated by numerous SRs and RCTs (76, 91-93, 95-106), with similar effect sizes among agents.(91-93, 95-106) Significant differences in side effects among agents occur, as well, including differences in the risk of sedation, EPS, metabolic effects, anticholinergic side effects, and cardiovascular effects. In an RCT by Ishigooka et al. (2021), there was no difference among aripiprazole, paliperidone, and blonanserin for remission and overall symptom severity per total Positive and Negative Syndrome Scale (PANSS) scores for second-line treatment with monotherapy.(115) Another RCT by Feng et al. (2020) found moderate quality data that demonstrated no difference between lurasidone and risperidone for overall symptom severity, positive symptoms, negative symptoms, illness severity, and global improvement per the CGI-I.(116) Another RCT by Shafti et al. (2014) found no difference between olanzapine and risperidone for positive symptoms and overall improvement in symptom severity per the CGI.(117) One RCT by Naber et al. (2015) found a greater improvement in symptom severity in patients with aripiprazole once monthly versus paliperidone palmitate once monthly, per the CGI-S from baseline to week 28.(118) This finding indicates that some patients might respond better to one antipsychotic over another, but this response is highly variable, unpredictable, and individualized among patients.(118) Evidence

suggests equivalent effectiveness among agents. To minimize polypharmacy, the Work Group suggests using another agent when patients do not respond to an initial course of treatment, rather than augmentation with a second agent and combination pharmacotherapy.

Patient preferences vary regarding a trial of another antipsychotic versus adding another agent. Some individuals with schizophrenia might hesitate to add or trial another medication because of additional side effects or non-response to the first agent trialed. Further, variations exist in methods of switching a patient from one antipsychotic to another, with little evidence to suggest one method is superior to another. Some providers might slowly cross-titrate from one antipsychotic to another, or some providers might prefer to stop and start a patient on a new medication with little to no cross-titration. This process is highly individualized based on various antipsychotic pharmacokinetic and pharmacodynamic properties and the antipsychotics involved as well as on patient and provider preferences. Before determining treatment failure and using another agent, ensuring an adequate treatment trial of a sufficient dose over a long enough duration is important. Additionally, ensuring acceptable antipsychotic adherence before switching agents is important, unless the patient is experiencing intolerable side effects. The definition of an adequate treatment trial is discussed further in Recommendation 12. Changing agents requires close monitoring because relapse or withdrawal symptoms can occur. Rather than switching to an alternative agent, the addition of another agent is an option; however, studies not included in the evidence base indicate antipsychotic polypharmacy has been associated with increased risk and severity of side effects and treatment non-adherence.(119, 120)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(76, 91-93, 95-106, 115-117) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including the risk of bias and imprecision. The benefits of monotherapy outweighed the potential harm of no medication, polypharmacy, or continuing a medication with significant adverse events. Individuals with schizophrenia who are not treated with antipsychotic medication can experience catastrophic outcomes, including homelessness, unemployment, and inability to care for themselves. Antipsychotic treatment is the cornerstone of treatment for schizophrenia. Patient values and preferences varied. Some patients might not want to take a medication if it causes distressing side effects and might want to try a different antipsychotic to manage their symptoms. Additionally, some patients might not want to take medication at all because of lack of effect, lack of insight, or beliefs about their medications, including causing stigma and shame. Thus, the Work Group made the following recommendation: 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.

Recommendation

11. We suggest offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests that treatment with long-acting injectable (LAI) antipsychotics improves adherence in patients with schizophrenia. Medication non-adherence in individuals with schizophrenia can be a barrier to treatment response and can significantly affect an individual's risk of hospitalization and relapse.(121) The evidence review identified one SR (32 RCTs, n=8,577) by Kishimoto et al. (2021).(121) The comparisons were mainly second-generation LAIs versus second-generation oral antipsychotics (OA) (18 RCTs; 56.3%) or first-generation LAIs versus first-generation OAs (nine RCTs; 28.1%). There were also subgroups of 65 cohort studies and 40 pre-post studies.

Findings suggest that patients receiving LAIs demonstrate higher levels of adherence rates than patients receiving OAs, as indicated by statistically significant differences ($p<0.0001$) in the mean Medication Adherence Rating Scale (MARS) and the proportion of patients with ≥75% days of adherence during the treatment period.(121)

There is a consideration that patients who volunteer for participation in RCTs might be more likely to adhere to their medication regimens, which could potentially obscure a difference in adherence between LAIs and OAs; however, this SR demonstrated greater adherence to LAIs in patients in both RCTs and cohort studies.(121) Of note, only two RCTs with fewer than 100 patients each contributed data to adherence outcomes.

Among important outcomes, LAIs were associated with fewer hospitalizations than OAs; however, no difference occurred in outcomes, such as symptom reduction, QoL, functional status, and treatment discontinuation. In an RCT not included in the evidence base nor impacting the strength of the recommendation, Noordraven et al. (2017) found that financial incentives can improve antipsychotic adherence compared with TAU.(122)

Patient preferences varied significantly regarding this treatment. Patients might prefer not to take an oral medication daily and, thus, might prefer an LAI because of ease of administration and no pill burden. Additionally, evidence suggests that patients have decreased hospitalization with LAIs, which might also be significantly preferential for patients when deciding between an LAI and an OA. If patients decline LAIs, some might be uncomfortable with needles or injections. Additionally, ensuring that the providers administering the injection are properly trained and informed on injection technique is important and can vary between practice settings and practitioner experience. The LAIs

have unique and varied preparation and administration techniques (e.g., duration the product must be shaken; injection speed; injection location; methods, such as Z-track for FGAs). Deviations from the directions in injection technique can significantly affect the pharmacokinetics of the medication, and, thus, the patient outcomes. Frequent visits to a clinic might be burdensome for the patient; however, they might also provide some benefits because the patient must be seen by a provider to receive the injection. Providers must establish tolerance to the oral version of the LAI before a trial of the LAI to ensure that the patient will not have intolerable side effects. Additionally, an initial trial of the oral antipsychotic version is essential to ensure that patients will respond to the medication. The half-life of the LAI varies significantly among agents and can be as high as 148–159 days. Therefore, switching patients' medication frequently can be challenging in the event of treatment non-response without confounding outcomes from another medication trial.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(121) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size, imprecision, and risk of bias because of the lack of blinding of personnel and participants. The benefits of LAIs, including greater adherence and lower rates of hospitalization, slightly outweighed the potential harm of any adverse events, resource use, or training needed to perform LAIs. Patient values and preferences were largely varied because some patients fear needles, feel concerned about lack of discipline and being able to take their medication daily, or prefer not to come into the clinic regularly for an injection. Conversely, some patients prefer not to take daily oral medications and, as a result, struggle with their adherence. Thus, the Work Group made the following recommendation: We suggest offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia.

Recommendation

12. We recommend the use of clozapine for individuals with treatment-resistant schizophrenia.
    (Strong for | Reviewed, New-added)

Discussion

Although definitions have varied over time and among studies, most recent discussions of treatment-resistant schizophrenia are based on the consensus guidelines developed in 2017 by the Treatment Response and Resistance in Psychosis (TRRIP) working group.(123) According to the TRRIP guidelines (not included in the evidence base), individuals with schizophrenia are considered treatment-resistant when they continue to experience at least moderate symptoms and impairments after at least two courses of treatment with different antipsychotic medications of adequate dose, duration (with at least six weeks at a target dose consistent with the effective doses specified in the Food

and Drug Administration [FDA] approved product labeling), and adherence. Recent studies (not included in the evidence base) estimate that approximately 20–25% of people who receive a diagnosis of schizophrenia will exhibit treatment resistance.(124, 125) However, the proportion is likely to be higher among people in clinical settings receiving ongoing care for schizophrenia as a chronic condition.

Evidence from an SR comparing clozapine with all other antipsychotic medications suggested that improvements for total psychotic symptoms, positive symptoms, and negative symptoms are greater for clozapine than for pooled estimates for other FGAs or SGAs in clinical trials with periods of observation up to three months.(126) Evidence evaluating responses over longer periods of observation suggested that improvements in positive, but not negative or total, symptoms were greater for clozapine than for other antipsychotic medications.(126) This review included studies using a definition of treatment resistance (failure to respond to at least one trial [and preferably two] of a FGA or an SGA) that might have been less stringent than the criteria suggested by the TRRIP working group.(123, 126) The GRADE rating for the evidence was moderate for evaluations of outcomes with timeframes of up to three months and for longer timeframes for positive symptoms only. The GRADE of evidence was low for evaluations over longer timeframes for other outcomes. These findings are consistent with the evidence that led to the FDA's 1989 approval of clozapine for treatment-resistant schizophrenia.

Another SR that focused on pairwise comparisons of antipsychotic medications for treatment-resistant schizophrenia found no differences between clozapine and chlorpromazine, haloperidol, risperidone, olanzapine, or ziprasidone in symptomatic outcomes.(127) The GRADE rating of the evidence included in this SR was low, and the SR included studies using a range of definitions for treatment resistance. Although sensitivity analyses suggested that the primary outcome did not differ among definitions of treatment resistance, the authors suggested that the lack of differences might have been a result of limited statistical power. The authors also speculated that the differences between their results and the findings that led to FDA approval for clozapine might have been because of changes over time in the quality of clinical trials, treatment histories for treatment-resistant patients, and increasing placebo responses that led to smaller drug-placebo differences. Nevertheless, possibly consistent with a unique role for clozapine, none of the pairwise comparisons suggested that any other medication led to greater improvements than clozapine.

Both SRs noted that clinically meaningful associations of clozapine plasma levels with clinical responses exist and that, for those studies reporting plasma levels, they appear to have been low.(126, 127) Both SRs speculate that this finding might have attenuated the differences between medications.

The FDA-approved product label for clozapine includes a Black Box warning emphasizing serious risks. The most important risks might be neutropenia and

agranulocytosis. To ensure that clozapine is not dispensed to patients without adequate monitoring for neutropenia, the FDA requires a Risk Evaluation and Mitigation Strategy (REMS); the Clozapine REMS program requires that all providers prescribing clozapine, all pharmacies dispensing it, and all individuals receiving it are registered and that all adhere to requirements for blood testing before prescribing and dispensing the medication.[e] Other possible adverse effects listed in Black Box warnings include orthostatic hypotension, bradycardia, and syncope; myocarditis and cardiomyopathy; and a dose-related increased risk of seizures.

Evidence about adverse effects from the SR comparing clozapine with other antipsychotic medications as a group suggested that seizures, sialorrhea, tachycardia, fever, dizziness, and sedation are more common in people receiving clozapine. It also suggested that insomnia is more common in people receiving other antipsychotic medications and that weight gain does not differ among medications.(126) The GRADE rating of the evidence for differences in adverse effects was moderate. Evidence from the SR on pairwise comparisons suggested that extrapyramidal symptoms were more common in people receiving risperidone than clozapine and that weight gain was more common in people receiving clozapine than risperidone.(127) The GRADE rating of the evidence for pairwise comparisons for adverse effects ranged from very low to moderate. In general, the review demonstrated relatively few significant differences, possibly related to limitations in sample sizes and statistical power. Of note, neither SR provided data regarding rare but potentially severe adverse events, including agranulocytosis, myocarditis, and cardiomyopathy, which are more common with clozapine, or neuroleptic malignant syndrome, which is more common with other antipsychotic medications.

Patient preferences vary significantly regarding clozapine treatment. The patient focus group noted that the treatment goals should encompass the foundational elements of being able to live, work, and learn. This philosophy is consistent with the use of clozapine for people with treatment-resistant schizophrenia to ensure that they have received a trial of the medication most effective for controlling their symptoms and the extent to which they interfere with recovery. However, clinical experience suggests that people with schizophrenia can be anxious about the rare but potentially serious adverse effects of clozapine and that they might experience the increased monitoring needed for its safe and effective use. As noted by the patient focus group, psychoeducation and shared decision making involving providers, patients, and families are vehicles for addressing the large variation in patient values and preferences and for achieving patient-centered treatment goals.

In evaluating the feasibility of implementing this recommendation, the Work Group recognized that translating the evidence currently available into operational criteria, specifying which people with schizophrenia should receive clozapine and when it should

[e] See: www.newclozapinerems.com/home

be prescribed, is difficult. The TRRIP working group definition of treatment resistance represents a significant advance.(123) However, it was developed to be used prospectively to inform the design of future research rather than for guiding the clinical application of the existing evidence. Furthermore, the guidelines were not included in the systematic evidence review. The sensitivity analysis included in the SR of pairwise differences might be useful as a guide to decision making. It suggested that estimates for the comparative effectiveness of clozapine and other antipsychotic medications did not appear to depend on the rigor of the criteria used to define treatment resistance.(127) This finding is consistent with findings from other studies (not included in the evidence base nor impacting the strength of the recommendation) suggesting that clozapine might be more effective than risperidone or haloperidol for the treatment of moderately refractory schizophrenia and that it should be considered "for some patients who do have some response to antipsychotics, but still experience troubling symptoms."(128, 129)

Resources required for the safe and effective use of clozapine include the capacities needed to meet FDA's regulatory requirements, including laboratory tests to monitor neutrophil levels; training for both pharmacies and prescribers; registration of pharmacies, prescribers, and patients; and reporting of episodes of neutropenia. Historic concerns that benign ethnic neutropenia (BEN) represented a barrier to the availability of clozapine for African American individuals with schizophrenia were addressed through modifications in the Clozapine REMS protocols for blood testing in people with BEN (not included in the evidence base nor impacting the strength of this recommendation).(130) Other resource-related issues include the need for increased clinical contacts, both after clozapine is started and after lapses in treatment, to allow for careful titration of the medication, starting at very low doses and increasing gradually.

As discussed previously, both SRs note that clinically useful associations exist between plasma levels of clozapine and its metabolites and clinical responses.(126, 127) Speculations have occurred that titrating doses to adjust plasma levels could enhance therapeutic benefits.(131, 132) Findings not included in the evidence base nor impacting the strength of the recommendation suggest that smoking increases the rate of clozapine metabolism. If people stop or cut down on smoking while remaining on a constant dose of clozapine, blood levels can be increased and toxic effects can result; if they start or restart smoking, levels can be decreased, and effectiveness can be reduced.(133) Moreover, evidence exists from Castberg et al. (2017; not included in the evidence base nor impacting the strength of the recommendation) that aging decreases the rate of clozapine metabolism.(134) At the same time, physiological changes related to aging increase the risks of several adverse effects. Therefore, safe, effective use of clozapine might require the availability of laboratory resources to evaluate blood levels and providers who have the training and knowledge required to interpret them.

The Work Group understood that the evidence related to this recommendation should be evaluated in the context of the limited options available for the pharmacologic

treatment of individuals with treatment-resistant schizophrenia. Specifically, the Work Group noted the importance of recognizing that schizophrenia is associated with significant decreases in life expectancy and that treatment-resistant schizophrenia might be the most disabling of all mental health conditions.(135, 136) In this context, evidence from epidemiological studies, not included in the evidence base nor impacting the strength of the recommendation, suggests that clozapine might have a unique role in preventing excess mortality;(137-140) these studies suggest that this effect might be related to the use of clozapine to treat schizophrenia or schizoaffective disorder with suicidality as well as to indirect effects on health and behavior mediated by its greater effectiveness for treating symptoms. In addition to effects on mortality, clozapine might have a role in ameliorating what otherwise might be a life-long disability.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*. (126, 127) (123, 126, 127) The Work Group's confidence in the quality of the evidence was moderate for several timeframes and outcomes but low for others; therefore, the overall confidence in the quality of the evidence was low. The body of evidence had serious limitations in the risk of bias. The Work Group considers the benefits of clozapine relative to other antipsychotic medications to outweigh the harms for people with treatment-resistant schizophrenia. Patient values and preferences varied significantly because of concerns about the risks of rare, serious adverse events and the burden of increased monitoring needed to support early recognition and prevention. However, the process of shared decision making could ensure that potential benefits, risks, and preferences are discussed and that individuals have the opportunity to make informed decisions about whether to accept treatment with clozapine. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted . . . when low quality evidence suggests benefit in a life-threatening situation," the Work Group made the following recommendation: We recommend the use of clozapine for individuals with treatment-resistant schizophrenia.

Recommendation

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)

Discussion

Evidence supports adding an SGA to clozapine monotherapy in individuals with clozapine-resistant, treatment-resistant schizophrenia. A high burden of disease exists for individuals with schizophrenia resistant to treatment with clozapine, and the evidence now shows that augmentation with a second antipsychotic medication is warranted. Clinical judgment and patient preference should also be considered in the case of a lack of response to clozapine, including the burden of the REMS. However,

the side effects of clozapine are significant. The evidence suggests augmenting clozapine with another second-generation antipsychotic medication. However, the discontinuation and consideration of other avenues of treatment, such as a different antipsychotic medication or procedural treatments (e.g., electroconvulsive therapy [ECT]), might be prudent (see Recommendation 25 and Recommendation 26 on neuromodulatory treatments). That the use of cognitive behavioral therapy (CBT) in clozapine-resistant patients improved PANSS scores but was less cost effective than TAU is noteworthy.(141) The consideration of FDA-approved medications or procedures, which are common practice, would be more likely candidates for treatment (see recommendations on non-pharmacologic interventions).

Bartoli et al. (2019) found that aripiprazole or ziprasidone added to clozapine was favored for depressive symptoms or for negative and depressive symptoms, respectively.(142) Siskind et al. (2018) found that aripiprazole added to clozapine was favored for negative symptoms and global psychopathology.(143) Ortiz-Orendain et al. (2017) found that risperidone added to clozapine was favored for positive symptoms.(144)

Patient values and preferences might vary regarding treatment with clozapine alone or with augmentation of clozapine. The use of clozapine alone can be burdensome because of the Clozapine REMS requirement of blood draws for monitoring the presence of dangerous neutropenia and cardiomyopathy. For some individuals, adding an SGA to augment clozapine for residual symptoms of clozapine-resistant schizophrenia might not represent an increased burden. However, for some patients, acceptability implications might be a factor when adding an SGA to clozapine because of the increased burden of side effects.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(142-144) The Work Group's confidence in the quality of the evidence was very low. For clozapine-resistant, treatment-resistant schizophrenia, the benefits of augmenting treatment with clozapine by adding a second-generation antipsychotic slightly outweighed the potential harms of adverse events or worsened symptoms. Caution and careful consideration of patient goals and side effect profiles should be considered. Patient values and preferences varied because some individuals might express concern over treatment with additional medications. Thus, the Work Group made the following recommendation: 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.

c. Pharmacologic Interventions for Treatment of Side Effects

Recommendation

14. There is insufficient evidence to recommend for or against any treatment for hyperprolactinemia-related side effects in individuals with schizophrenia. **(Neither for nor against | Reviewed, New-added)**

Discussion

The evidence review identified two RCTs that evaluated the effects of medication on hyperprolactinemia because of antipsychotic medication.(145, 146) An RCT by Kelly et al. (2018) evaluated the effects of adjunctive aripiprazole on hyperprolactinemia and its related symptoms in premenopausal women taking antipsychotic medication (n=46).(145) Patients were randomized to receive 5–15 mg of aripiprazole in addition to their antipsychotic medication for 16 weeks and were compared to placebo (continuation of their antipsychotic treatment). The RCT found no difference in outcomes related to the resumption of normal menstruation and the Female Sexual Distress Scale-Revised but found a benefit for the normalization of galactorrhea and sexual dysfunction. Also found was a statistically significant difference in prolactin level normalization among groups.(145) In another RCT by Zhou et al. (2021),10 mg/day of adjunctive aripiprazole was compared with a high dose of vitamin B6 (600 mg/day) for the treatment of antipsychotic-induced hyperprolactinemia in male patients with treatment-resistant schizophrenia (n=200).(146) Both treatment groups reported a statistically significant reduction in serum prolactin through week 16 in patients with hyperprolactinemia; however, symptoms associated with hyperprolactinemia were not measured or reported.

A meta-analysis by Li et al. (2013; not included in the evidence base nor impacting the strength of the recommendation) reported a statistically significant reduction in prolactin levels when aripiprazole was added to a antipsychotic medication (n=639).(147) Two of the studies included in the meta-analysis reported prolactin-related symptoms in their outcomes; however, the confidence in the quality of the evidence was very low and reported inconsistent resolution of prolactin-related symptoms in addition to small sample sizes. No differences in side effects and treatment discontinuation between groups were found.

Zhou et al. (2021) reported increased incidence of akathisia, dizziness, hand tremor, and orthostatic hypotension in patients randomized to adjunctive aripiprazole, although Kelly et al. (2018) reported no significant differences in side effects between treatment groups as described above.(145, 146) Concern about antipsychotic polypharmacy exists when adding aripiprazole to another antipsychotic because of the risk of compounding any metabolic side effects, EPS, sedation, or orthostatic hypotension.

Patient preferences vary regarding treatment for hyperprolactinemia. If patients find symptoms related to hyperprolactinemia (e.g., a galactorrhea, sexual dysfunction,

menstrual irregularities) distressing, treatment to mitigate these symptoms might be highly desirable, even if it entails taking an additional antipsychotic or other medication. Monitoring long-term bone mineral density (BMD) might be warranted in patients with sustained hyperprolactinemia because of the effects of prolactin on BMD. Treatment of hyperprolactinemia might be burdensome because of the risk of additional side effects with the addition of adjunctive aripiprazole. Amantadine and bromocriptine have also been suggested as possible treatments for hyperprolactinemia. In addition, some patients and providers might determine that the side effect burden and risk of sustained hyperprolactinemia might outweigh the benefits of a patient's current antipsychotic regimen, determining that switching to an alternative agent with lesser risk of hyperprolactinemia is preferable.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(145, 146) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes, risk of bias, and imprecision. The benefits of adding medications to treat hyperprolactinemia were balanced with the potential harms. Patient values and preferences varied because of the range in the effect of hyperprolactinemia on symptoms and QoL. The amount of distress from hyperprolactinemia can vary widely for patients, and the added burden of an additional medication might also vary from patient to patient. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against any treatment for hyperprolactinemia-related side effects of antipsychotic medications in individuals with schizophrenia.

Recommendation

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)

Discussion

The use of augmenting agents should be considered in the context of alternative strategies for managing obesity, including exercise and other behavioral interventions and counseling about lifestyle modifications (see Recommendation 40) as well as changing the antipsychotic medication to one that is less likely to cause weight gain and other metabolic side effects.

Vancampfort et al. (2019) conducted a review of meta-analyses that systematically and quantitatively analyzed pharmacologic interventions that have been studied to improve weight loss in patients with schizophrenia.(148) Changes in metabolic symptoms, such as weight loss and reduction in waist circumference, were observed with the use of metformin, topiramate, and aripiprazole (metformin: 29 trials, n=1,279; topiramate: 15 trials, n=783; aripiprazole: 9 trials, n=813), all with medium effect size.

Sabaghi et al. (2019) conducted an RCT (n=66) of patients with obesity and schizophrenia or schizoaffective disorder examining the effects of metformin as an adjunctive therapy for weight loss.(149) Mean weight changes were noted to be -3.50 kg for the intervention group and +4 kg for the control group.

Overall findings from the evidence assessing the benefits of adjunctive augmentation of pharmacologic agents (e.g., metformin, topiramate, aripiprazole) suggest that a reduction in weight and a reduction in waist circumference occurs. The evidence implies that, compared with placebo or non-adjunctive therapy, patients experience moderate benefits from these agents. The meta-analyses completed by Vancampfort et al. (2019) also suggest that patients in some instances benefit from adding one of these agents versus switching to another antipsychotic agent.(148) Augmenting versus switching is recommended to be considered on an individual basis because some antipsychotics, such as oanzapine, might result in dysregulation of glucose, in which case switching might be best.

Other factors the Work Group considered were variations in patient values and preferences. Some patients might resist taking additional medications, whereas others might prefer an additional medication for weight loss over lifestyle changes, such as diet changes, exercise, or both. Other implications include acceptability and feasibility of adjunctive therapy in this population, such as concern over additional medication and the fact that all options are readily available.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(148, 149) The Work Group's confidence in the quality of evidence was moderate. The benefits of using metformin, topiramate, or aripiprazole as an augmenting agent for weight loss slightly outweighed the harms or burdens of use or both. There was concern regarding the adverse cognitive effects of using topiramate as well as the increased risk of congenital anomalies, low birth weight, and low vitamin K with resultant bleeding risk in pregnant women. Metformin was found to be the augmenting agent used most frequently in clinical practice. Patient values and preferences vary because some patients might resist additional medications, although others might prefer weight loss treatment via medication rather than lifestyle change. Thus, the Work Group made the following recommendation: We suggest using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia.

Recommendation

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)

Discussion

Tardive dyskinesia (TD), a movement disorder associated with the long-term use of dopamine receptor-blocking agents, can be severe and disabling. TD causes loss of muscle control, especially of the face, arms, and legs, which become stiff and jerky. Evidence suggests that vesicular monoamine transporter 2 (VMAT-2) inhibitors improve abnormal involuntary movement scale (AIMS) scores and severity of TD symptoms in individuals with schizophrenia and TD. Kane et al. (2017) evaluated 150 individuals with schizophrenia or schizoaffective disorder who received a ≥1 dose of treatment with valbenazine during a six-week, double-blind, placebo-controlled study.(150) They found that treatment with valbenazine improved AIMS scores for patients who received 40 mg as well as for those who received 80 mg (AIMS least squares mean changes from baseline; 80 mg: -2.9 [p<0.0001], 40 mg: -1.6 [p<0.01]; placebo: 0.3 [not significant]). AIMS response (≥50% total score improvement from baseline) also favored valbenazine (80 mg: 40.9%, 40 mg: 26.2%; placebo: 9.3%). However, the clinical global impression of change—tardive dyskinesia (CGI-TD) scores and response rates for valbenazine versus placebo showed no statistical difference.(150)

Artukoglu et al. (2020) evaluated the efficacy of pharmacologic treatments for TD in an SR and meta-analysis.(151) Three trials (n=346) of VMAT-2 inhibitors were identified. Overall, VMAT-2 inhibitors were associated with a significantly greater score reduction compared with placebo (Standardized Mean Difference [SMD]: 0.63+/-0.11; 95% CI: 0.41 – 0.85; p<0.005). Individual trials also showed benefit compared with placebo. The trials with deutetrabenazine and valbenazine were of higher quality compared with the trials with tetrabenazine. However, these agents all possess a similar mechanism of action.

Evidence for the use of benzodiazepines and phenobarbital,(152) vitamin B6,(153) and vitamin E was reviewed, but the evidence was insufficient to recommend any of these agents.(154) No evidence was retrieved citing the use of clozapine or quetiapine, antipsychotics with a low potential to cause TD, as adjunctive agents or as alternative monotherapy for the management of TD.

Patient preference varies slightly regarding this treatment because most patients with distressing TD likely desire treatment with an agent generally well tolerated. However, these agents are costly and represent a potential resource burden for the individual with TD as well as for the health care system. Further, attention to the equitable use of these agents is warranted. Because SGAs are commonly used to treat schizophrenia and schizoaffective disorder and possess a lower likelihood of causing TD compared with FGAs, the need for and use of VMAT-2 inhibitors for the management of disabling TD might decrease.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(150-154) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some

limitations, including a small sample size, risk of bias, and study imprecision and indirectness.(150) The benefits of improving AIMS scores in individuals with schizophrenia or schizoaffective disorder and TD outweighed the potential harms, which were minimal. Patient values and preferences were similar because most patients who have distressing tardive dyskinesia would likely want treatment with an agent that is generally well tolerated. Thus, the Work Group made the following recommendation: We suggest a trial of a vesicular monoamine transporter 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia

Recommendation

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)

Discussion

Clozapine-induced sialorrhea might be disabling, adversely impact QoL, cause physical and psychological complications, and reduce adherence. Although atropine eyedrops given sublingually and ipratropium nasal spray used sublingually are commonly provided in clinical practice, evidence suggests that treatment with diphenhydramine improves clozapine-induced sialorrhea in individuals with schizophrenia. Chen et al. (2019) conducted an SR and meta-analysis of 19 studies on treatment strategies for clozapine-induced sialorrhea.(155) Antimuscarinics (propantheline, six studies; glycopyrrolate, one study; benzhexol [trihexyphenidyl], one study; ipratropium bromide, one study) and antihistamines (diphenhydramine, five studies; chlorpheniramine, two studies; cyproheptadine, one study; astemizole, two studies) were evaluated.(155) When considered as a class, antimuscarinics were superior to placebo (RR: 2.22; 95% CI: 1.58–3.11; p<0.001, I^2: 66%). However, the risk ratio of the class was largely driven by studies with propantheline, which is no longer available in the U.S. Benzhexol also provided benefit, but the sample size was small (n=30). Similarly, when antihistamines were considered as a class, results were positive with an RR of 2.76 (95% CI: 1.78–4.29; p<0.001; I^2: 80%). Within the antihistamine class, only diphenhydramine had a sufficient sample size (five RCTs, n=334) on which to base a recommendation. Patients in this study receiving diphenhydramine were significantly more likely to experience a reduction in sialorrhea compared with those who received a placebo (RR: 3.01; 95% CI: 1.61–5.63; I^2: 83%; p=0.0001).

Patient preferences regarding this treatment vary. Some patients would find sialorrhea distressing and want to treat it, although others might be troubled by the possible side effects of adding diphenhydramine to their drug regimen. Potential side effects of diphenhydramine include the risk of increased sedation, GI issues (e.g., constipation), and cognitive impairment. Diphenhydramine is listed on the American Geriatrics Society Beers Criteria as an “avoid” medication in older adults. Chen et al. (2019) reviewed four studies that provided data on the rates of constipation with diphenhydramine. They

found that no statistically significant difference in rates occurred between intervention and placebo groups, and a number needed to harm of 35.(155) Nevertheless, recognizing that clozapine has potent anticholinergic effects and can result in central nervous system and peripheral anticholinergic toxicity is essential. The risks of adding an additional anticholinergic medication should be addressed through psychoeducation and shared decision making, and treatment planning should consider adding bowel regimens.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(155) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including risk of bias and inconsistency of data.(155) The benefits of diphenhydramine to improve clozapine-induced sialorrhea slightly outweighed the potential harms (e.g., adverse events). Patient values and preferences varied because of the concern for potential cognitive and GI side effects of combining diphenhydramine with clozapine. Thus, the Work Group made the following recommendation: We suggest a trial of diphenhydramine for individuals with schizophrenia who are experiencing sialorrhea as a side effect of clozapine.

Recommendation

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)

Discussion

Cognitive impairments are a strong predictor of poor functional outcomes in individuals with schizophrenia.(156) Negative symptoms constitute a heavy burden, are present in at least 50% of individuals with schizophrenia, and are associated with poor social and role functioning, reduced QoL, and low recovery rates.(157) Studies of non-antipsychotic medications have examined N-methyl-D-aspartate (NMDA) functioning on GABAergic and glutamatergic receptors, muscarinic and nicotinic cholinergic agents, and nicotinic pathways in the treatment of cognitive impairments in schizophrenia. Evidence across eight SRs showed mixed findings regarding improvement in cognitive and negative symptoms with any non-antipsychotic medications.(156-163)

One SR of seven RCTs included in Kuppili et al. (2021) found that augmentation with d-cycloserine (DCS) was not associated with any significant improvement in cognitive and negative symptoms.(158) However, DCS also targets NMDA glutamatergic receptors. Preclinical research has shown improvements in memory consolidation, recall, and visual recognition when NMDA glutamatergic receptors are activated, suggesting some promise for agents in the treatment of cognitive impairments in schizophrenia that might also target the NMDA receptor.(158) Six RCTs included in Koola et al. (2020) found augmentation with galantamine, which influences cholinergic and NMDA cortical

pathways, was associated with improvement in cognitive symptoms but no improvement in negative symptoms.(156) Three additional RCTs included in Kuppili et al. (2021) found no associated improvement in negative symptoms with N-acetylcysteine augmentation.(158)

One SR examined the neuroprotective effects of N-acetylcysteine, an antioxidant, measuring clinical efficacy on improvement in negative symptoms.(161) Adjunctive N-acetylcysteine showed no improvement in negative symptoms.

Twenty-five RCTs included in the SR by Chang et al. (2019) found augmentation with mixed NMDA glutamate receptor (NMDAR) enhancing agents (i.e., benzoate, CXC515, D-serine, DCS, minocycline, N-acetylcysteine, pregnenolone, L-carnosine, sarcosine, glycine) showed no associated improvement in cognitive and negative symptoms.(162)

Sabe et al. (2021), which included nine RCTs, found augmentation with oxytocin >40 IU was associated with improvements in negative symptoms.(157) Nine RCTs included in de Boer et al. (2018) found augmentation with raloxifene, an estrogenergic agent, was associated with improvement in cognitive symptoms.(163) Premenopausal women had fewer psychotic and negative symptoms, better cognitive and social functioning, and fewer hospitalizations with raloxifene treatment compared with TAU. The role of estrogen is believed to be protective. Additionally, higher estrogen levels are strongly correlated with better cognitive performance in women with schizophrenia (women without schizophrenia were not considered).(163)

Although some studies found some improvement in cognitive and negative symptoms, the confidence in the quality of evidence was very low. The benefits and harms, burdens, or both associated with the augmentation of non-antipsychotic medications in the treatment of cognitive and negative symptoms was balanced. Patient preferences varied for certain medications. Subgroup considerations include individuals with seizures, pregnant or lactating women, and differences in effect on acute versus chronic schizophrenia.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(156-163) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small number of studies, significant attrition rates, risk of allocation concealment, and incomplete outcome data. The benefits of augmentation with non-antipsychotic medications in the treatment of cognitive and negative symptoms were balanced with the potential harms. Evidence of benefit was found for certain outcomes but largely essentially no effect. Patient values and preferences varied somewhat because of differing medication preferences. Thus, the Work Group made the following recommendation: 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.

d. Non-pharmacologic Interventions

Recommendation

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)

Discussion

Given the shift toward community-based care, caregivers often take on roles, such as care managers or care coordinators, for which they might have limited knowledge, training, or both. Ashcroft et al. (2018) completed a meta-analysis for caregiver-directed psychosocial interventions (CDPI) for individuals with schizophrenia chronic psychiatric illnesses versus TAU.(164) CDPIs are described as interventions seeking to (a) construct an alliance between the caregiver and person with schizophrenia; (b) reduce adverse family atmosphere (i.e., lowering the emotional climate in the family by reducing the stress and burden on relatives); (c) enhance the capacity of caregivers to anticipate and solve problems; (d) reduce expressions of anger and guilt by the family; (e) maintain reasonable expectations for patient performance; (f) encourage relatives to set and keep to appropriate limits while maintaining some degree of separation, when needed; and (g) attain a desirable change in the caregiver's behavior and belief system. CDPIs are interventions used to train, assist, and support caregivers to enhance their capacity to anticipate and solve problems, to increase a positive family environment prevent burnout, and to strengthen relationships with those in their care. Specific to schizophrenia, these programs range from providing general information on the psychiatric condition and treatment to comprehensive interventions that include psychoeducation, consultation, family interventions, and therapies. Findings suggest that CDPIs improve outcomes related to relapse and hospitalization rates in individuals with schizophrenia.(164) Ashcroft et al. (2018) observed no statistically significant differences in other outcomes, such as medication non-adherence, suicide attempts, and death when comparing CDPIs with TAU.(164) Benefits of CDPIs outweigh the possible harms associated with the intervention because no harms were identified in the systematic evidence review. Through training in CDPIs, caregivers are better positioned to effectively negotiate treatment adherence. Variations in patient preference for treatment might also exist because of the level of caregiver involvement the patient desires. Study findings indicated that the overall wellbeing of individuals with schizophrenia improved with programs that held a component of caregiver training intervention. CDPIs were noted to decrease caregiver emotional burden, decrease rates of relapse and hospital room visits for the individual with a schizophrenia patient, and improve other non-medication–related behaviors in the patients' care. Participants in the study included persons age 18 or older with schizophrenia or schizophreniform diagnosis. No specific mention was made of active duty Service members, military, or Veteran status. The study indicated improved caregiver presentation outcomes through

decreased stress, QoL, and financial strain. The systematic evidence review indicated no significant impact on medication adherence. The overall effects favoring CDPIs were significant in three of the four outcome categories. Whereas the positive effects of CDPIs also diminished with time for two outcomes: relapse and hospitalization. It has been previously observed (Pharoah et al. 2010; Okpokoro et al. 2014) that the effects of the intervention diminish during the follow-up period where no intervention is received. However, based on the trends, CDPIs were still favored, so it is possible the patient or caregiver attrition or both played a role in the lack of statistical significance across follow-up times. The follow-up stratified outcomes were most frequently available 0–12 months, which was the only follow-up subgroup with significant differences between CDPIs and TAU.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(164) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had limitations, including small sample size and confounders in the analysis. The benefits of CDPIs outweighed the harms, such as time burden on the primary support person and the distress that these conversations can cause. Patient values and preferences varied somewhat because some patients prefer little-to-no family involvement in their care or cannot involve family members in their treatment plan. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

The key critical elements of the traditional Assertive Community Treatment (ACT) model include a medication prescriber, a shared caseload among team members, direct service provision, high frequency of patient contact, low patient-to-staff ratios, and outreach to patients in the community. Two RCTs provided moderate quality evidence on adapted versions of ACT, which included many (but not all) of the traditional elements. These studies found improvements across a range of outcomes, including decreased hospitalizations and rates of relapse and improvement in functional status and symptom reduction.(165, 166) Specifically, based on the current research evaluated, Luo et al. (2019) found that those receiving the adapted ACT model of care were less likely to be readmitted to the hospital and had fewer mean days to readmission compared with TAU. Botha et al. (2014) also found that patients receiving the adapted ACT had fewer readmissions compared with those receiving TAU.(166)

Luo et al. (2019) also found that those receiving the adapted model of ACT also had significant functional improvements (e.g., better rates of reemployment and reductions in general, positive, and negative symptoms).(165)

A robust body of additional evidence lends further support for the standard model of ACT; however, it was not included in the systematic evidence review conducted as part of this CPG update because it was published before the timeframe for the evidence review.(167) Additional evidence not included in the evidence base nor impacting the strength of the recommendation found that standard ACT is efficacious in decreasing homelessness and improving housing stability.(167-170)

In considering the use of the ACT models examined in the current evidence base, the Work Group determined that the benefits outweigh the harms because no harms were identified. Regarding individual values and preferences, the Work Group notes that preference for this service model might vary across the perceived need for the high level of intense service delivery associated with the examined ACT models in the current evidence base.

In VHA, adaptations of ACT include Mental Health Intensive Case Management (MHICM), Rural Access Network for Growth Enhancement (RANGE), and Enhanced Rural Access Network for Growth Enhancement (E-RANGE), collectively referred to as ICMHR Services (Intensive Community Mental Health Recovery).[f]

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(165, 166) The Work Group's confidence in the quality of evidence was moderate. The body of evidence had some limitations, including a lack of studies conducted within populations in the U.S. The benefits of the examined ACT models outweighed the harms because no harm was identified in the evidence base. Patient values and preferences varied somewhat because some individuals with schizophrenia have different preferences for their treatment. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

[f] Available at: https://www.va.gov/VHAPUBLICATIONS/ViewPublication.asp?pub_ID=3164

Discussion

As described by Bond et al. (2014; not included in the evidence base nor impacting the strength of the recommendation), the Individual Placement and Support (IPS) model is a model of supported employment designed to help individuals gain and maintain competitive employment.(83) The evidence supporting this model includes studies supporting its use for people with FEP (considered separately in Recommendation 5) (171-174) as well as others, suggesting that IPS is superior to usual services for individuals with schizophrenia on a range of employment domains, including achievement of competitive employment and hours and weeks worked in competitive employment.(175, 176) The study by Twamley et al. (2012) also measured days until competitive employment but found no difference between groups. No harms of participation in IPS have been identified.(175) However, although VA entitlements are protected when Veterans are engaged in a VA IPS program, a loss of non-VA entitlements might occur for individuals who obtain paid competitive employment. For this reason, benefits counseling is considered a key feature of the model.

Participant preferences vary because participation is predicated on an individual's interest in obtaining competitive employment. According to Bond et al. (2014), approximately 65% of individuals with a serious mental illness (SMI) wish to be employed, but only 15% are employed.(83) The provision of IPS is consistent with the results of this CPG's patient focus group (see Appendix F), in which a primary theme was that "goals should encompass foundational elements of being able to live, work and learn." The studies in the evidence review suggest that IPS is appropriate for individuals across the age span because as Twamley et al. (2012) included individuals age 45 or older.(175) IPS is an intensive support model, designed to be integrated into mental health treatment, and requires a trained workforce able to work with individuals with psychiatric disabilities as well as with employers in community businesses. The "place then train" model of IPS-supported employment can differ from how vocational rehabilitation specialists are traditionally educated and trained. The need for a high level of service intensity, a strong interdisciplinary team approach, and a community-based service delivery model means that it can be challenging to implement IPS to fidelity and maintain high levels of fidelity to the model over time. Although it was not included in the evidence base, studies indicate that strategies to support implementation exist, but they can be resource intensive.(88, 177)

IPS is required in VA by VHA Directive 1163 but is not currently available in DoD; modification of existing rules and regulations would be necessary to implement it in DoD.[g] Currently, no research is examining the feasibility and effectiveness of IPS in DoD, either individually or as part of a coordinated VA and DoD FEP program.

Three RCTs of IPS with augmentation were identified as part of the evidence base. Glynn et al. (2017) compared IPS, enhanced with a skills training approach called

[g] Available at: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=8438

workplace fundamentals, with a standard IPS program with no TAU condition; however, the evidence was of low quality, and no differences were detected on critical outcomes.(178) Zhang et al. (2017) conducted an RCT also comparing a work-related social skills training augmentation of IPS with a standard IPS condition.(179) Although some significant differences occurred in critical outcomes favoring the enhanced IPS intervention, the evidence was of low quality. Combined with the lack of difference in the Glynn et al. (2017) study, the Work Group did not make a recommendation specifically related to IPS enhanced with skills training.(178, 179) A third study examined cognitive remediation combined with a supported employment program that did not follow the IPS model.(180) Although this RCT found benefits to the combined supported employment and cognitive remediation condition, the evidence was very low, and the model differed somewhat from IPS. Therefore, the Work Group did not make a recommendation based on this single trial. Additionally, one study by Kukla et al. (2018), which combined cognitive remediation, work-oriented CBT, and vocational services as usual, found some benefit in the critical outcomes of number of hours worked and a provider-rated measure of work performance when compared with work-oriented CBT alone and a separate group of vocational services alone.(181) However, this study had a small sample size and was of low quality. The vocational model was not IPS, and, therefore, this evidence could not be combined with other studies in the evidence review, and the Work Group did not make a separate recommendation related to this intervention. Additional research on IPS includes adaptations and augmentations (not considered as part of the evidence base for the recommendation). Some of a large body of studies of heterogeneous populations (not included in the evidence base nor impacting the strength of this recommendation) combine IPS with other interventions, such as cognitive remediation or motivational interviewing.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(174-176, 178-181) The Work Group's confidence in the quality of the evidence was moderate. The Work Group noted that some studies included in Hellström et al. (2021) were conducted outside the U.S., possibly limiting generalizability.(176) The benefits of IPS to improve employment outcomes outweigh the potential harms because no adverse events have been noted in the evidence base. Patient values and preferences varied, given that employment might not be a goal of every individual with schizophrenia and given that paid employment might lead to negative impacts on entitlements outside the VA setting. Thus, the Work Group made the following recommendation: We recommend the use of the Individual Placement and Support model of supported employment for individuals with schizophrenia with a goal of employment.

Recommendation

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)

Discussion

Housing First is a well-defined model developed by Pathways to Housing in New York City, combining housing, comprehensive services (typically delivered by ACT teams), and recovery-oriented principles to support individuals with chronic homelessness.(182) In a Housing First model, individuals are assisted with obtaining independent housing, usually in apartments, while simultaneously being assisted with mental health and substance use treatment; no readiness requirements apply. It differs from "treatment first" models in which individuals are placed in other forms of supported housing while being treated for their mental health conditions and comorbidities, including substance use disorders, with the assumption that they are unready for independent housing until they stabilize.

Two studies were included in the systematic evidence review. The first was a large (n=703) RCT of Housing First compared with TAU in France.(183) In the Housing First group, individuals were offered scattered site Housing First, defined as housing combined with ACT, and were followed for two years. Individuals randomized to Housing First experienced greater housing stability. They spent significantly fewer days hospitalized than those in TAU, but the quality of evidence was very low and was not a critical outcome. Additionally, there were no significant differences in emergency department visits, hospital admissions, length of stay, or medication adherence for individuals receiving Housing First versus TAU.(183) A second study was a three-arm RCT conducted in Canada comparing TAU with two active treatments: congregate Housing First with onsite supports and scattered site Housing First with ACT, followed for an average of 2.6 years.(184) No significant differences were found between the congregate Housing First and TAU on any outcomes. A significant improvement in medication adherence occurred favoring the scattered site Housing First over TAU, but this result was not considered a critical outcome, and the quality of the evidence was very low.(184)

A long history of research on variants of Housing First models shows evidence for their effectiveness in heterogeneous populations, including individuals with mental health conditions. For example, Stergiopoulos et al. (2015; not included in the evidence base nor impacting the strength of the recommendation) found that a Canadian scatter site model using MHICM (rather than ACT) improved housing stability over TAU in a heterogeneous group of homeless adults with mental illness (not included in the evidence base nor impacting the strength of the recommendation).(185) An SR by Woodhall-Melnik et al. (2016; not included in the evidence base nor impacting the

strength of the recommendation) of Housing First studies concluded that the evidence was strong for housing related outcomes, but more research on non-housing outcomes and subpopulations is necessary, and that generalizing across different countries should be done with caution (not included in the evidence base nor impacting the strength of the recommendation).(186)

DoD provides housing to active duty Service members, and as such, interventions such as Housing First might be unnecessary. VA has a robust array of services for individuals who are homeless or unstably housed. In one such model, VA, in partnership with the Department of Housing and Urban Development (HUD), uses a housing first philosophy that includes permanent supported housing, provided through vouchers from HUD, together with case management, provided by VA, through the HUD-VA Supported Housing program (HUD-VASH). The goal of the HUD-VASH program is to ensure that Veterans have housing when they need it, eliminating barriers to care, while concurrently providing the comprehensive treatment and supports necessary for health and wellbeing.[h] Housing First is also emphasized as an important model in the federal strategy for ending homelessness in the U.S.(187)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(183, 184) The Work Group's confidence in the quality of the evidence was very low. The body of evidence supporting Housing First specifically for people with schizophrenia had limitations, including studies conducted outside the U.S. In a Tinland et al. (2020) study, the proportion of individuals with diagnoses of schizophrenia was 70%, below the typical cutoff of 80% for inclusion in a systematic review.(183) However, even based on this limited evidence, the benefits of Housing First appear to outweigh the potential harm because no evidence of harm was identified. Patient values and preferences varied somewhat because some individuals do not prefer to live in traditional housing. Finally, regarding resource use and equity concerns, a dearth of low-income housing exists across the country, especially in more rural areas. The Work Group recognizes that safe, stable housing is a basic human right and that it can be central to wellbeing and recovery for individuals with schizophrenia. Thus, given the low quality of the evidence for the benefits of Housing First versus other strategies specifically for individuals with schizophrenia, the Work Group made the following recommendation: There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with schizophrenia experiencing housing insecurity.

Recommendation

23. We suggest cognitive training programs for the treatment of cognitive impairment and negative symptoms for individuals with schizophrenia.
    (Weak for | Reviewed, New-added)

[h] https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=5437

Discussion

Cognitive remediation training is an evidenced-based non-pharmacologic treatment for the neurocognitive deficits seen in schizophrenia (not included in the evidence base nor impacting the strength of this recommendation).(188) Cognitive remediation training can be effective in improving concentration, memory, and problem solving as well as in reducing positive symptoms of schizophrenia (not included in the evidence base nor impacting the strength of this recommendation).(189) Limited evidence is currently available to support the use of compensatory cognitive remediation or training programs in treating cognitive impairment for individuals with schizophrenia. The Work Group examined evidence from four RCTs and one SR that concentrated on various cognitive remediation modalities.(190-194)

Two RCTs examined the Integrative Cognitive Remediation Program (REHACOP),(193, 194) which combines neurocognitive remediation, social cognitive intervention, and functional skills training. Individuals in the studies attended treatment three times a week for 60–90 minute sessions. Both RCTs found that REHACOP in conjunction with TAU reduced negative symptoms, social cognitive impairment (Happe Test, SFRT, BLERT), and non-social cognitive impairment (e.g., speed of processing, verbal memory, working memory, problem solving) at from 4–5 month follow-up.(193, 194) Both studies also showed improvements in social functioning (UPSA) at 4–5 month follow-up.(193, 194) Pena et al. (2018) also found that REHACOP with TAU can improve functional status (GAF).(194)

The effectiveness of Cognitive Remediation Therapy (CRT) was evaluated by one SR (n=8,851) of 130 RCTs.(190) The review found that CRTs improved global and social cognition and reduced negative symptoms and non-social cognitive impairment between 3–4 weeks of follow-up.

An RCT by Zhu et al. (2021) examined the effects of compensatory cognitive training (CCT) and medication self-management skills training (MSST; n=72).(191) CCT combined with MSST was superior to TAU in reducing negative symptoms, cognitive impairment, and non-social cognitive impairment over the course of three months.(191) However, CCT compared with TAU showed no difference in negative symptoms.

An RCT (n=53) conducted in France compared the benefits of RECOS, a Cognitive Remediation for Psychosis program, on access to employment and work attendance for people with schizophrenia.(192) The small sample size found that at eight weeks, RECOS used with TAU exhibited improvements in vocational functioning and social functioning with a reduction in non-social cognitive symptoms and negative symptoms.(192) Although the RECOS findings were promising, this study was smaller and of lower quality.

Patient preferences vary significantly regarding cognitive remediation and training programs. Because of the time intensity of this intervention, some individuals and their

families might not contribute the amount of time necessary for the training to succeed. The patient focus group noted that although cognitive remediation can benefit individuals with schizophrenia, it can be burdensome because of the time required. Some patients are unwilling to commit to frequent travel time and lengthy treatment visits, which could result in missing work or social obligations.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(190-194) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and a majority of the RCTs were rated as poor quality.(191-194) The benefits of CRT and compensatory cognitive training programs (reduction of negative symptoms, social cognition impairment, non-social cognitive impairment with improvement in functional status, vocational functioning, and social functioning) slightly outweighed the time intensity of treatment. Patient values and preferences varied significantly because of treatment frequency and length. Thus, the Work Group made the following recommendation: We suggest compensatory cognitive training programs for the treatment of cognitive impairment for individuals with schizophrenia.

Recommendation

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)

Discussion

The evidence supporting this treatment suggestion comes from studies that evaluated various forms and combinations of skills training interventions. The interventions varied widely in content, combination, and focus but generally included conventional social skills training, cognitive behavioral social skills training, supportive goal skills training, social cognition training, and life skills training. Intervention strategies included behaviorally based instruction (e.g., breaking skills down into component parts), role modeling and practice or rehearsal opportunities, and encouragement for home practice. One SR that focused on a range of psychosocial interventions and their impact on relapse prevention included four studies relating to skills interventions; none had significant findings relating to the outcomes of relapse, functional decline, dropout rate, and noncompliance.(195) In contrast, a single SR of 25 RCTs comparing any type of social skills training with any comparator and with TAU(196) as well as 10 small RCTs(193, 194, 197-204) that looked at a range of skills interventions generally found reductions in overall symptoms and negative symptoms. Some studies also found that skills training improved social cognitive impairment,(193, 194, 204) facial and emotional recognition skills,(200) and social and general skills functioning.(194, 196, 197, 199)

In considering the use of skills training, the Work Group determined that the benefits outweighed the harms because no harms were identified in the systematic evidence review. Patient values and preferences vary somewhat because of individual preferences, although the patient population demonstrated a general acceptance of skill interventions. Skills training interventions are widely available in VA, including the national rollout of social skills training,

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(193-202, 204) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations relating to the small sample sizes across the evidence base and a range of methodological flaws, including problems with masking and blinding of the outcome assessor and lack of follow-up. Another important weakness in the evidence was the absence of consideration for more proximal outcomes of skill performance. It should be noted, however, that in a meta-analysis of conventional social skills training (published before the search window for the current CPG systematic evidence review and, therefore, not impacting the strength of the recommendation), skills training produced significant effects on proximal measures of skill (i.e., evidenced in role-play tests) and more distal measures of community functioning.(205) Thus, the Work Group made the following recommendation: 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.

Additional research should focus on how best to encourage the generalization of newly learned skills by individuals with schizophrenia to their everyday environments. Future work must examine the effectiveness of remote delivery of skills training using virtual technology.

Recommendation

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)

Discussion

Evidence on the effectiveness of transcranial direct current stimulation (tDCS) in reducing negative symptoms in schizophrenia or other psychotic disorders (e.g., schizoaffective disorder, delusional disorder) included one SR with 15 constituent RCTs. These RCTs reported 16 trials comparing tDCS+TAU to sham+TAU.(206) An analysis of 14 trials reporting negative symptoms showed a significant reduction in these symptoms as measured by the PANSS negative subscale scores in the active group versus sham groups, with follow-up for up to three months. These findings were also maintained in trials of individuals with a diagnosis of schizophrenia only and in trials using two treatment sessions per day. When evaluating adverse effects, no statistically

significant differences in complaints were found between the two groups in acute mood change; burning sensation under the electrodes; daytime sedation, sleepiness, or both; headache; itchiness under electrodes; neck pain; pricking or tingling under the electrodes; scalp pain, head pressure, or both; skin flush, redness, or both under the electrodes; tinnitus; or trouble in concentration.

This recommendation relates to negative symptoms only. Although included in the systematic evidence review, Guttesen et al. (2021) was not included as part of the evidence base supporting this recommendation because of lack of applicability; the study looked at a reduction in verbal auditory hallucinations.(207)

Another SR and network meta-analysis by Tseng et al. (2022; not included in the evidence base nor impacting the strength of this recommendation) identified seven RCTs related to tDCS.(208) They reported that compared with sham control interventions (allowing concurrent treatment with antipsychotics during the study period), anodal tDCS was associated with significantly greater improvements in negative symptom severity than sham control (SMDs:
-1.28; 95% CI for categorical data: -2.55–0.05).

The evidence comparing repetitive transcranial magnetic stimulation (rTMS) alone or combined with other psychopharmacologic interventions is mixed, showing no significant difference in their overall benefit for the treatment of individuals with schizophrenia.(207, 209, 210) In rTMS, a magnetic field is generated by using a rapidly fluctuating electrical current.

Repetitive transcranial magnetic stimulation was associated with possible benefits in an RCT by Lu et al. (2021) that compared rTMS plus oral risperidone (n=70) to oral risperidone alone (n=70). At the six-month follow-up, the combination of rTMS and risperidone was associated with a 94.3% improvement in PANSS total score in 66 patients in the active group compared with an 81.4% improvement in 57 patients in the control group.(211) There was also evidence for an impact of rTMS on cognitive functioning and both homocysteine (Hcy) and brain-derived neurotrophic factor levels.(211)

More research is needed on neuro-imaging guided rTMS with variability in pulse characteristics. The research should consider the response to specified courses of treatment and interventions that could maintain benefits over time.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(206-211) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a lack of allocation concealment in some constituent RCTs. The benefits of tDCS, reduction in negative symptoms were balanced with the adverse effects identified by the evidence base, including acute mood changes, burning sensations, sleepiness, sedation, headaches, neck pain, and itchiness. Patient values

and preferences varied largely because some patients might prefer to pursue treatment that does not include neuromodulatory techniques. Other patients might have heard of and want to try these interventions. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against transcranial direct current stimulation and repetitive transcranial magnetic stimulation for individuals with schizophrenia.

Recommendation

26. There is insufficient evidence to recommend for or against electroconvulsive therapy for individuals with schizophrenia.
    (Neither for nor against | Reviewed, New-added)

Discussion

The evidence comparing electroconvulsive therapy (ECT) alone or combined with other psychopharmacologic interventions is mixed, showing no significant difference in their overall benefit for the treatment of individuals with schizophrenia.(212) Although not included in the evidence base nor impacting the strength of this recommendation, Petrides et al. (2019; a secondary analysis of an included study, Petrides et al. [2015])(213) also had mixed findings for ECT augmentation.(214) ECT consists of generating a seizure by administering an electrical stimulus via electrodes placed either unilaterally or bilaterally on the scalp.

Although the evidence does not support a recommendation for the use of this intervention, there were some suggestions of specific contexts in which they might be effective. ECT showed some potential benefits for individuals with clozapine-resistant schizophrenia when used as an augmentation strategy for clozapine. A 2019 randomized, single-blind, eight-week study by Petrides et al. (2019) compared patients with clozapine-resistant schizophrenia with TAU (clozapine group, n=19) versus a course of bilateral ECT plus clozapine (ECT plus clozapine group, n=20) versus TAU (clozapine group, n=19) in patients with clozapine-resistant schizophrenia.(214) At eight weeks, half of the individuals (n=10) in the ECT plus clozapine group showed at least a 40% reduction in symptoms based on the BPRS psychotic subscale. In contrast, none of the individuals in the clozapine group met the reduction of symptom criterion.(214) Additionally, 47.4% of the individuals in the crossover phase met the symptom reduction criteria.(214) One of the limitations of this study was the small sample size. Petrides et al. (2019) found no significant difference in side effects between the two groups.(214)

More research is needed on ECT. The research should consider the response to specified courses of treatment and interventions that could maintain benefits over time.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(212) The Work Group's confidence in the quality of evidence was very low. The benefits and harm, burden, or both of ECT were balanced. Patient values and preferences varied somewhat because

some patients might be more likely to try these interventions, although others might hesitate. Other implications considered were the resource intensiveness of these interventions and the feasibility of these interventions for both VA and DoD. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against electroconvulsive therapy for individuals with schizophrenia.

Recommendation

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)

Discussion

The evidence reviewed lacks sufficient strength to recommend for or against the use of any specific psychosocial intervention explicitly aimed at preventing or treating non-adherence to antipsychotic medications in patients with schizophrenia. Six studies (n=2,287) of six different intervention strategies were reviewed. All interventions showed a level of benefit in a variety of areas but none in the critical outcomes for this CPG.

Chien et al. (2016; n=134) showed that the addition of motivational interviewing to TAU had benefits at 18 months follow-up with regard to improved adherence to medication.(215) However, Barkhof et al. (2013; n=114) showed no difference in adherence with motivational interviewing versus control with 12 months follow-up.(216) Symptom reduction, as assessed with the PANSS, showed mixed results for motivational interviewing. Chien et al. (2016), Barkhof et al. (2013), and Bröms et al. (2020; n=202) all showed no difference in the absolute rate of hospitalization.(215-217) A study on shared decision making by Hamann et al. (2017) showed no significant effect on adherence.(218) Zou et al. (2013) studied adherence as a critical outcome and found that when greater than 10 treatment sessions of self-management education were performed, medication adherence improved compared with when fewer than 10 sessions were performed.(219) Additional data referenced in other sections also favored self-management education over TAU.(84, 164) An RCT by Noordraven et al. (2017; not included in the evidence base nor impacting the strength of this recommendation) found that financial incentives can improve antipsychotic adherence compared with TAU.(122)

Patient values and preferences likely vary little when using psychosocial interventions for medication adherence. Patients are mostly accepting of motivational interviewing and shared decision making. Some might be suspicious of financial incentives to improve medication adherence. The patient focus group participant noted that a variety of models of care can be helpful because psychosocial interventions work additively in many cases (see Appendix F). Further, the patient focus group participant did not specifically mention any particular benefit regarding modality for improving medication adherence.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(215-219) The Work Group's confidence in the quality of the evidence was very low. The benefits of motivational interviewing, shared decision making, and self-management education for improving the critical outcome of medication adherence were balanced with the potential harm of unchanged rates of hospitalization rates. Patient values and preferences were similar because some patients prefer non-invasive treatments. Thus, the Work Group made the following recommendation: 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.

Recommendation

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.
    (Weak for | Reviewed, New-added)

Discussion

Clubhouses are a model of psychiatric rehabilitation designed to foster community and support meaningful activities for individuals with psychiatric disabilities. Clubhouses are accredited by Clubhouse International, a non-profit international organization that supports Clubhouse programs with training and quality assurance.[i] Accredited Clubhouses function as a partnership between staff and members to run the Clubhouse as part of a "work-ordered day." Among other functions, Clubhouses offer employment services, such as transitional work, supported employment, and independent employment support.(220, 221)

One SR of the Clubhouse model for individuals with schizophrenia was identified in the systematic evidence review.(222) Although Yan et al. (2021) identified seven RCTs (n=682) for meta-analysis, all seven RCTs were conducted in China and only one, Chen et al. (2020; n=49), reported employment outcomes. No statistically significant difference in employment outcomes was found between the Clubhouse and the control group, though the sample size was likely too small to detect meaningful differences. The Work Group's confidence in the quality of evidence was very low because the evidence was from a single study with a small sample size and challenges exist with generalizability because of cultural differences. Therefore, no recommendation could be made for or against the Clubhouse model for improving employment outcomes.

The Work Group noted that the Yan et al. (2021) meta-analysis identified differences favoring the Clubhouse model on several non-vocational outcomes, including social

[i] See https://clubhouse-intl.org/

functioning, QoL, and symptoms for individuals with schizophrenia who participated in general (not employment-specific) Clubhouse services.(222)

Patient preferences regarding Clubhouse employment services vary because not all individuals have employment as a goal. No adverse effects of Clubhouse participation were identified. As a vocational model, however, insufficient evidence exists to support the achievement of employment outcomes, and, thus, there is the potential risk that individuals with schizophrenia might engage in Clubhouse employment services without benefit. As listed above, Clubhouse participation might have other psychosocial benefits, suggesting that potential benefits and harms are balanced. For several reasons, an accredited Clubhouse would likely be difficult to implement in the VA/DoD. Legislation would be necessary to give VA and DoD the authority to offer Clubhouse programs. Further, Clubhouses are non-hierarchical community-based models in which staff and members have equal roles in the activities of the Clubhouse, which would likely require significant culture change to implement fully. Thus, both feasibility and acceptability are potential concerns.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(222) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size and limited generalizability. The benefits of Clubhouse programs for employment outcomes were balanced with the potential harm. Patient values and preferences varied somewhat because not all individuals have a goal of employment. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

The evidence base for this recommendation included two small, poor-quality RCTs that focused narrowly on providing peer support, supplemental resources, and skills training to help bridge the transition from inpatient hospitalization to living in the community.(223, 224) Both of these studies had limitations because of lack of clarity around randomization, allocation concealment, blinding of participants, study personnel, assessors, and high attrition. The evidence base also included one SR that incorporated two additional fair-quality RCTs that both focused on participants' use of social media and peer support forums.(174) Per Välimäki et al. (2016), the methodological quality of these two studies varied.(174) Limitations included incomplete details regarding the sequence and allocation concealment and lack of blinding (although due to the nature of

the intervention). The literature on which this recommendation is based is extremely limited because of the restrictions on studies meeting the criteria for inclusion in the systematic evidence review.

In considering the use of peer-provided interventions, the Work Group determined that the benefits outweigh the harms because no direct harms were identified in the evidence base. Patient values and preferences varied; some individuals might not want peer support, might prefer professional services, or might want neither. However, recent survey data (not included in the evidence base and, therefore, not impacting the strength of this recommendation) found that peer support was specifically named as a preferred service among Veterans discharged from psychiatric inpatient units.(173)

Additional studies (albeit with methodological shortcomings), not included in the evidence base nor impacting the strength of this recommendation, suggest that general peer support and peer-led interventions have a positive impact on recovery, QoL, and other related outcomes, including hopefulness, empowerment, social support, treatment engagement, and internalized stigma reduction.(171, 172, 225-227)

Of further note, the Work Group considers peer support a value-based practice and one that should be maintained. Of note, VA has committed to the development of a large (1,300+) peer workforce that delivers both peer support and structured or well-specified interventions or both to Veterans across the care continuum. Further, VHA Directive 1163 mandates that peer support services must be available for all Veterans patients for whom this service is clinically indicated, especially for those with serious mental illnesses.[j] Funding for and accessibility of peer support, however, might be less available outside VA and currently is unavailable in DoD.

Finally, the Work Group recommends additional research to evaluate the effects and impacts associated with peer support. A research agenda advancing the field could include empirically testing theoretical mechanisms of peer support, developing fidelity measures, conducting more rigorous outcome studies focusing on a broad range of both service-related and individual outcomes, and involving peers in the design and execution of research.(227) Given the substantial peer workforce in VA, it is also recommended that future work focuses on related issues of how best to implement peer services and advance both in-person as well as remote technology peer-supported interventions.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(174, 223, 224) The Work Group's confidence in the quality of evidence was very low. The Work Group noted that the benefits outweighed the harms for peer support interventions because no harms were identified in the evidence base. Patient values and preferences varied because some patients might not want peer support. Thus, the Work Group made the following

[j] Available at: https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=8438

recommendation: There is insufficient evidence to recommend for or against the use of peer-provided interventions for individuals with schizophrenia.

Recommendation

30. We suggest adding aerobic exercise to treatment as usual to reduce symptoms for individuals with schizophrenia.**(Weak for | Reviewed, New-added)**

Discussion

Antipsychotic medications are effective in treating the positive symptoms of schizophrenia; however, diminishing negative symptoms associated with poorer functional outcomes has posed a challenge. Evidence suggests aerobic exercise (e.g., playing sports, brisk walking, jogging, cycling, row machine, treadmill, elliptical) in conjunction with TAU improves QoL and positive and negative symptoms in individuals with schizophrenia or schizophrenia-related disorders.(228-230)

A meta-analysis of 22 studies (n=1,249) by Vogel et al. (2019) found that aerobic exercise and TAU (antipsychotic medication therapy) resulted in a significant reduction in negative symptoms from 3–35 weeks follow-up compared with TAU alone.(230) Evidence from Sabe et al. (2020) in a meta-analysis of 17 RCTs (n=954) and Vogel et al. (2019) found that aerobic exercise as adjunctive treatment was associated with a reduction of negative symptoms from 10–96 weeks or 3–35 weeks follow-up when compared with occupational therapy, toning exercises, or table soccer in conjunction with TAU versus TAU alone.(229, 230) A meta-analysis of 29 studies (n=1,109) by Dauwan et al. (2016) found an overall significant effect on total symptom severity and a medium effect on both negative and positive symptoms.(228) A relatively small RCT (n=53) by Kern et al. (2020) similarly found that aerobic exercise in addition to TAU improves negative and positive symptoms.(231) No effect on cognition was noted. Variations were noted in the effects of group and individual aerobic exercise, with more robust effects noted in individuals involved in supervised exercise programs consisting of exercise 30 minutes per day, three times per week for at least 12 weeks. Exercise adherence was highest for individuals with schizophrenia in programs that were supervised and structured.

Evidence suggests that exercise improves overall health. Patients can benefit from a reduction in blood pressure, stabilization of glucose levels, weight loss, sleep promotion, improved cognition, and prevention or stabilization of cardiopulmonary diseases. Patient preferences varied regarding this treatment. The patient focus group participant noted that, although aerobic exercise is recommended for general overall health, it can be burdensome because some patients are unwilling or unable to exercise. Further, some variation might occur in the applicability of individuals with co-occurring conditions. Other implications include individuals' varying levels of comfort or ability to exercise in their community because of lack of access and safety concerns in certain geographic locations.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(228-231) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including high heterogeneity, small effect size, and lack of focus on primary or predominantly negative symptoms.(229, 230) The benefits of aerobic exercise on negative and positive symptom reduction and QoL outweighed the potential harm of minor physical injury. Patient values and preferences varied because some individuals prefer not to exercise. Thus, the Work Group made the following recommendation: We suggest adding aerobic exercise to treatment as usual to reduce symptoms and improve functioning for individuals with schizophrenia.

Recommendation

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)

Discussion

Evidence suggests that yoga, which typically involves a series of physical postures, breathing techniques, and mindfulness practices designed to unite the body and mind, improves negative and positive symptoms, QoL, and medication adherence in individuals with schizophrenia.(232) Two SRs found that treatment with yoga was associated with improvements in negative symptoms and positive symptoms.(230, 233) Furthermore, two smaller, lower-quality studies found that yoga improves QoL and medication adherence.(232, 234) None of the studies reported harmful effects from yoga.

Patient preference regarding yoga varies. A slight possibility of physical injury exists during the practice of yoga, although no injuries were reported in these studies. Furthermore, the quality of the evidence reviewed was low for the improvement of positive and negative symptoms and very low for the improvement of QoL and medication adherence. The addition of yoga was not shown to improve functioning or the Positive and Negative Symptom Scale total score.(233, 234)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(230, 232-234) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including small sample sizes, imprecision (230, 232, 234), and inconsistency.(233) That being the case, the benefits of yoga (e.g., improvements in positive and negative symptoms, QoL, medication adherence) outweighed the small potential for injury. Patient values and preferences varied somewhat because some patients might be uninterested in including yoga in their treatment plan. Thus, the Work Group made the following recommendation: We suggest offering yoga as an adjunct to other evidence-based treatments for positive and negative symptoms for individuals with schizophrenia.

Recommendation

32. We suggest cognitive behavioral therapy for psychosis in combination with pharmacotherapy for individuals with prodromal and early psychosis. **(Weak for | Reviewed, New added)**

Discussion

Evidence suggests that cognitive behavioral therapy for psychosis (CBTp) combined with pharmacotherapy is efficacious in treating individuals with prodromal and early psychosis; research has shown that outcomes in chronic diseases can be improved with early symptom identification and initiation of treatment. CBTp is an evidence-based therapy used to improve QoL and reduce the distress caused by symptoms of psychosis, such as paranoia, worry, and insomnia. Similar to other forms of CBT, it is structured, time limited, and goal oriented. As the use of CBTp has expanded, multiple protocols have emerged, and it can be delineated into levels of treatment, ranging from 16 (or more) sessions to very specific interventions, such as those tailored for command hallucinations, to other CBT-informed interventions. Generally, the focus is on exploring and restructuring developed beliefs about distressing psychotic experiences and promoting behavior change to reduce maladaptive safety behaviors, encourage participation in care, and use coping strategies. Choice of psychotherapies should be based on a process of shared decision making that considers the benefits of available therapies and patient preferences.

Multiple studies suggest that CBTp combined with pharmacotherapy is efficacious in decreasing psychotic symptoms, improving QoL, and improving overall functioning across the course of disease process in schizophrenia (i.e., prodromal symptoms, early psychosis, and individuals with a diagnosis of schizophrenia).(235, 236) Zheng et al. (2022) found that in individuals at clinical high risk of psychosis, CBTp had a positive effect on reducing the rate of transition to a psychotic disorder and the attenuation of psychotic symptoms from 6–24 months post-treatment.(236) Turner et al. (2020) found a reduction in positive symptoms of psychosis with CBTp.(235)

Some variation exists in individual preferences regarding CBTp. The individual in the patient focus group noted that psychotherapy is unsuitable for everyone with this diagnosis, and some individuals might prefer to use pharmacotherapy only instead of combined with therapy. Individuals might or might not appreciate the structure or homework associated with CBT. Others might have difficulty finding a therapist trained in using CBT in individuals diagnosed with schizophrenia because it does require additional (but available) training. Individuals might also lack the resources needed to attend therapy appointments regularly because weekly psychotherapy could result in having to miss work or family or other social obligations.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(235-237) The Work Group's confidence in the quality of evidence was very low. The body of evidence had

limitations, including a small sample size, difficulty standardizing the population of interest, and difficulty with head-to-head comparisons based on the variability of the patient population, interventions applied, duration of intervention, time to follow-up, and treatment outcomes. The wide variation in critical outcomes made synthesizing the findings difficult because few direct comparisons were available. Some studies were likely excluded from the record review because their population of interest was too broad (i.e., they also included mood disorders with psychotic features) to be included in this review. The benefits of CBTp combined with pharmacotherapy in individuals with prodromal and early psychosis outweighed the potential harms because psychotherapy is considered a safe intervention. Patient values and preferences varied somewhat because not all patients want to engage in psychotherapy owing to the time requirement, structured nature of the modality, or associated homework. Thus, the Work Group made the following recommendation: we suggest cognitive behavioral therapy for psychosis in combination with pharmacotherapy for individuals with prodromal and early psychosis.

Recommendation

33. We suggest the following psychotherapies and psychotherapeutic interventions in combination with pharmacotherapy for individuals with schizophrenia:
    - Cognitive behavioral therapy for psychosis,
    - Acceptance and mindfulness-based therapies,
    - Metacognitive therapy, or
    - Positive psychology interventions.

    (Weak for | Reviewed, New-added)

Discussion

Cognitive Behavioral Therapy and Cognitive Behavioral Therapy for Psychosis

Evidence suggests that CBT or CBTp combined with pharmacotherapy is efficacious in treating individuals with schizophrenia. CBTp, like other forms of CBT, is structured, time limited, and goal oriented. In CBTp, however, the focus is generally on exploring and restructuring the beliefs that individuals with schizophrenia have developed about their psychotic experiences that cause distress. Choice of psychotherapies should be based on a process of shared decision making that considers the benefits of the therapies available and patient preferences.

Bighelli et al. (2021) looked at CBTp and found that, when compared with TAU, CBT showed improvement in overall positive and negative symptoms.(195) Evidence existed, as well, that CBT reduced functional decline. However, when CBT was compared with other interventions (e.g., acceptance and commitment therapy, psychoeducation, supportive therapy, social skills training), no difference was observed in the outcomes. This suggests that the combination of pharmacotherapy with any of the other therapeutic modalities listed above, not just CBT, would benefit this population. Another RCT reported by both Morrison et al. (2018) and Law et al. (2017) showed that

CBT, in conjunction with pharmacotherapy, reduced global psychopathology overall and negative symptoms. (141, 238)

Multiple studies suggest that CBTp combined with pharmacotherapy is efficacious in decreasing psychotic symptoms, improving QoL, and improving overall functioning across the course of disease process in schizophrenia (i.e., prodromal symptoms, early psychosis, and individuals with a diagnosis of schizophrenia). Zheng et al. (2022) found that CBTp had a positive effect on reducing the rate of transition to a psychotic disorder and the attenuation of psychotic symptoms when looking at the interval of 6–24 months of follow-up in patients at clinical high risk of psychosis.(236) Turner et al. (2020) found a reduction in positive symptoms with CBTp.(235)

Acceptance and Mindfulness-Based Psychotherapies

Evidence suggests that combined with pharmacotherapy, acceptance and mindfulness-based psychotherapies reduce hospitalization, psychotic symptoms, and symptoms of depression in individuals with schizophrenia.(239) Acceptance and mindfulness-based therapies are best described as part of the "third wave" cognitive and behavioral therapies. As defined by Hayes and Hoffman et al. (2021), the third wave consists of psychotherapies "targeting the relationship of the client to his/her own experience."(240) The intent is to help the individual examine the function of internal processes and learn to live more effectively with the full spectrum of emotion and cognition. Acceptance in the context of these therapies is defined as the "willingness to experience affect without needless escape, avoidance or constraint."(240) Mindfulness is defined as, "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally."(241)

The acceptance and mindfulness-based psychotherapies included in the evidence review for this recommendation include ACT, Mindfulness-Based Stress Reduction (MBSR), Integrated Coping Awareness Therapy (I-CAT), Mindfulness-Based Crisis Intervention, and a Mindfulness-Based Psychoeducation Program (MBPP). Some studies examined the addition of a mindfulness intervention to an existing standard intervention as the active control. One study on progressive muscle relaxation (PMR) was also included in the evidence review.

Jansen et al. (2020) conducted an SR and meta-analysis on 16 studies of acceptance and mindfulness-based therapies.(242) The therapies included ACT, MBSR, mindfulness psychoeducation, and mindfulness interventions, all delivered in a group format. The meta-analysis revealed that acceptance and mindfulness-based psychotherapies had moderate effects on participants, demonstrating a reduction of hospitalization and a shorter duration of days hospitalized. Jansen et al. (2020) revealed large effects, as well, for the reduction of overall symptomatology for participants in both the short- and long-term.(242) Also found were small to moderate effects on depressive symptoms, social functioning, and negative symptoms. Additionally, the meta-analysis determined that mindfulness had a significant effect on QoL. Preliminary data indicates

that readmission rates were lower for the mindfulness-based crisis intervention group at 12 months, suggesting that lower readmission could be a potential outcome for this intervention. One RCT by Lopez-Navarro et al. (2020) found that the addition of a mindfulness-based intervention to pharmacotherapy (60-minute mindfulness sessions, including experiential practice and psychoeducation) might improve inhibitory control in individuals with schizophrenia and showed higher scores on self-report mindfulness measures.(243)

PMR is often used as a mindfulness-based intervention in third wave psychotherapies.(244) Lu et al. (2020) conducted an RCT and found PMR to significantly impact anxiety, symptoms of psychosis, and QoL post-intervention, though no difference was observed at the three-month follow-up.(244)

MBSR is an eight-session protocol developed by Jon Kabat-Zinn in 1979, initially designed to help individuals living with chronic physical illness cope with stress.(245) MBSR has been shown to have applications for those with chronic pain (246) and emotional distress.(247) An RCT conducted by Özdemir et al. (2022) demonstrated that mindfulness-based stress reduction is associated with improved hope, psychological wellbeing, and functional recovery over psychoeducation in individuals with schizophrenia.(248)

Lam et al. (2020) studied the impact of an MBPP-based off the original MBSR protocol.(249) The MBPP consists of eight 90-minute sessions addressing four key components, with all sessions including at least 20 minutes of mindfulness practice and a group discussion. The results showed significant improvements in emotion reappraisal and a reduction in depression and psychotic symptoms.

I-CAT is a manualized psychosocial treatment targeting allostatic load (an accumulation of chronic stress that overwhelms coping abilities). It uses a combination of positive psychology and mindfulness to increase positive emotions and increase resiliency.(250) Halverson et al. (2021) administered 14–24 sessions weekly to participants from a first break clinic (n=19).(250) I-CAT was more effective than TAU in maintaining employment and school social function. In addition, I-CAT yielded a significant reduction in symptoms and improved mindfulness and wellbeing compared with TAU; however, it did not show significant reduction in stress reactivity.

Metacognitive Therapy

Developed for individuals with schizophrenia, Metacognitive therapy (MCT) is an intervention consisting of manualized group training aiming to increase cognitive awareness (meta-level) via psychoeducation on cognitive bias and structured cognitive exercises. Evidence suggests that MCT, combined with pharmacotherapy, improves outcomes related to positive symptoms and cognitive symptoms in individuals with schizophrenia.(239, 251-254). Chen et al. (2021) noted that preliminary evidence favors the usefulness of MCT as a complementary tool for the community-based rehabilitation

of individuals with schizophrenia.(254) A study by de Pinho et al. (2021) assessed the efficacy and feasibility of providing MCT to individuals with schizophrenia by mental health nurses.(252) Results demonstrated that MCT effectively improved delusions and social function over time and immediately reduced hallucinations post-treatment.(252) Ishikawa et al. (2020) tested the efficacy of a new 10-module MCT that revealed effectiveness on positive symptomatology and improved general function.(251) Further investigation is needed on the long-term effects of MCT on cognitive bias.(251) According to Beck et al. (2004), cognitive insight is a core metacognitive domain that refers to the individuals' ability to evaluate and correct their own distorted beliefs and misinterpretations (self-reflectiveness) and the tendency to be overconfident in one's conclusions (self-certainty). According to Lopez-Morinigo et al. (2020), metacognitive interventions, specifically MCT, improve insight in individuals with schizophrenia spectrum disorders, notably cognitive insight shortly following treatment.(239) Long-term RCTs are needed to establish whether changes in insight related to metacognitive interventions are maintained over an extended period or result in improved outcomes. Lastly, Zonp et al. (2022) studied the effectiveness of MCT on impairment in social cognition in individuals with schizophrenia who were being treated by mental health nurses in a community mental health center. The study indicated that MCT conducted by mental health nurses was a safe, effective, practitioner-friendly program specific to social cognition.(253)

The Work Group reviewed findings from one additional study that investigated standard Metacognitive Reflection and Insight Therapy (MERIT) compared with tailored MERIT, in which the intervention—traditionally offered as an in-person psychotherapy—was enhanced via app-based technology.(255) Although the benefits of using tailored MERIT seemed to outweigh the harms, the Work Group chose not to make a recommendation specific to app-based technologies because of the limited evidence in this area.

Study findings indicate that MCT interventions improve positive symptomology, including delusions, social functioning, social cognitions, and general functioning. Based on the evidence identified, the Work Group suggests MCT combined with pharmacotherapy for individuals with schizophrenia.(239, 251-254)

Positive Psychology Interventions

Evidence suggests that positive psychology interventions will improve wellbeing and overall symptom reduction, including positive and negative symptoms, depressive symptoms, and QoL in individuals with schizophrenia. Initially developed for people who did not have a mental health diagnosis, the goal of positive psychology interventions is to achieve recovery in more facets than just symptom remission. The methods used to accomplish this goal vary among programs but generally focus on processes that will improve or optimize how people feel and function, leading to an indirect improvement of symptomatology.(256) One meta-analysis (nine studies, four of which were controlled) was identified in the literature search that specifically looked at positive psychology

interventions as an intervention for schizophrenia spectrum disorders.(257) It found that when combined with psychopharmacology, positive psychology interventions were efficacious in improving outcomes that were related to wellbeing, although noting that high-quality research with structured protocols using positive psychology techniques is required.

The quality of the evidence for the psychotherapies included in this recommendation ranged from low to very low. The wide variation in critical outcomes on CBT and CBTp made synthesizing the findings difficult because few direct comparisons were available. Some studies were likely excluded from the record review because their population of interest was too broad (i.e., they also included mood disorders with psychotic features) to be included in this review. Additional limitations include small sample size, population heterogeneity, intervention duration, time to follow-up, and treatment outcomes. Accessibility and feasibility of CBT in the VA/DoD setting is good because many practitioners are trained in this evidence-based psychotherapy, though fewer providers are trained in CBTp. The body of evidence on acceptance and mindfulness-based therapies include limitations, such as small sample size and risk of bias.(195, 242) Jacobsen et al. (2020) found that mindfulness-based interventions based on ACT delivered in an acute inpatient hospital setting are both feasible and acceptable to both patients and the staff.(258) Acceptance and mindfulness-based therapies are widely accessible among the active duty Service member and Veteran population because most providers are trained in at least one of these modalities. Limitations in the MCT evidence review include quasi-experimental design, size of the evidence base, and study population. Concerns surrounding feasibility include the need for providers to be trained in MCT; such providers are not readily available at all sites in VA and DoD settings. The primary limitation for positive psychology interventions is the small size of the evidence base. Notably, the patient focus group participant observed that non-pharmacologic treatments, including psychotherapy, are essential for developing coping skills to manage symptoms of schizophrenia.

The Work Group systematically reviewed evidence related to these recommendations. Therefore, they are categorized as *Reviewed, New-added*.(141, 195, 235, 236, 238, 239, 242-244, 248-255, 257, 258) The Work Group's confidence in the quality of evidence ranged from low to very low. The body of evidence had some limitations, which varied across psychotherapy models. Limitations in the CBT and CBTp studies include small sample size, population heterogeneity, duration of intervention, time to follow-up, and treatment outcomes. The evidence limitations on acceptance and mindfulness-based interventions include small sample size and risk of bias,(195, 242) while limitations for MCT and positive psychology interventions reflect the small evidence base. Patient values and preferences varied. Some individuals might prefer solely pharmacologic intervention without psychotherapy or psychosocial or recovery-oriented treatment, might prefer a different form of psychotherapy, or might decline treatment altogether. The psychotherapies included in this recommendation are

deemed generally acceptable to both patients and practitioners. However, feasibility of implementation varies based on provider training. For instance, although most VA/DoD practitioners have training in CBT, acceptance and mindfulness-based psychotherapies, or both, providers trained in CBTp or MCT might be limited. The benefits of CBT and CBTp, acceptance and mindfulness-based psychotherapies, MCT, and positive psychology interventions outweighed the potential harms and burdens (e.g., attending treatment) because psychotherapy is considered a safe intervention. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

Illness Management and Recovery (IMR) is a curriculum-based intervention based on the stress-vulnerability model. IMR is designed to teach and assist individuals with severe mental illness by teaching effective strategies to manage their disorders. The curriculum can be taught individually or in a group format and contains 11 topic modules on illness management strategies, including psychoeducation, relapse prevention, social skills training, and coping skills training.(259) The intention of IMR is to help individuals become more active in their treatment and make both objective and subjective gains in recovery while reducing acute hospitalization and crisis services.

The evidence reviewed for this CPG included three RCTs with patient populations from VA, Denmark, and Turkey.(259-261) Another RCT used the same data from the initial Danish RCT to review different outcome measures.(262)

Two of the RCTs compared IMR with an active control, and one study compared IMR with a TAU condition. No significant differences were found when IMR was compared with TAU in the domains of symptom severity, functional status, or social status.(261-263) When compared with an active control, IMR showed no significant differences related to symptom severity nor positive, negative, or cognitive symptoms, either immediately or at the nine-month follow-up.(259) Additionally, Jensen et al. (2019) found no differences between IMR and TAU conditions in clinical or personal recovery,

illness self-management, or service use at the one-year follow-up.(263) Although fidelity was high in this study, lower participation in the IMR group was a limitation.

One small RCT, conducted in Turkey by Polit et al. (2019), found that IMR produced improvement in social function compared with the face-to-face interview control group, as measured by the pro-social activities subscale at post-test and one-month follow-up.(260) Given the small number of participants in this study, the short timeframe for follow-up, and the hospital-based environment in which the study was conducted, the Work Group's confidence in the durability and generalizability of this finding is very low.

Patient values and preferences vary regarding this treatment because the ability to accept a diagnosis of schizophrenia and the desire to engage in treatment vary among individuals. The patient focus group participant noted that psychoeducation is beneficial for understanding the diagnosis of schizophrenia. They also emphasized the importance of being taught life skills and coping strategies as a means to effective recovery. The benefits and burdens of IMR appear to be balanced because IMR demonstrates no significant benefit over either TAU or similar curriculum-based modalities. Based on the systematic evidence review, IMR apparently provides equivalent benefits compared with TAU. Furthermore, the burdens of IMR are similar to comparable treatments. One consideration might be the duration of the program, which ranges from 3–10 months, with a longer duration being a potential barrier to implementation. Another potential implication of using IMR might be a requirement for training, providers, materials, and time allocation, which could be difficult to support in all settings.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(259-263) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size,(260) low patient participation,(259) loss of participants to follow-up,(263) and lack of information on outcome assessor blinding. The benefits of IMR were balanced with the potential burdens. Patient values and preferences varied somewhat because some patients are uninterested in treatments for their diagnosis of schizophrenia. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against Illness Management and Recovery in combination with pharmacotherapy for individuals with schizophrenia.

Recommendation

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)**

Discussion

Virtual reality (VR) can be described as a modernized computer-simulated real-time three-dimensional virtual experience. In avatar therapy (AT), a computer-generated

audio-visual character is used to establish a conversation between the person with schizophrenia and the voices the person hears to help them cope with those voices.(264) Insufficient evidence was included in the systematic evidence review to recommend for or against AT.

An SR by Aali et al. (2020) of 12 studies, including three RCTs (n=195), found that although AT does not improve positive, negative, and general symptom severity (as measured by the PANSS) or reduce relapse rates when compared with TAU at seven weeks follow-up, improvement was seen in total Psychotic Symptom Rating Scales (PSYRATS) and QoL scores in the AT group.(264) The confidence in the quality of the evidence was very low because of the high risk of bias. None of the studies reported information related to general functioning, cognitive functioning, or economic outcomes. Clarke et al. (2019) conducted an SR of 21 RCTs (n=1,535) examining the effect of digital health technologies on psychotic symptoms. Low-quality evidence favored AT over control conditions (largely passive comparators, including TAU, with several active controls) in the improvement of psychotic symptoms (PANSS, PSYRATS, and the Paranoid Thoughts Scale) at 3–6 months.(265) Additionally, another SR of three RCTs (n=156) evaluated the effects of VR to support treatment compliance. The results of the study found that VR interventions failed to improve any cognitive functioning or treatment adherence outcomes at six weeks and 5–12 weeks.(266)

Patient values and preferences vary regarding this treatment. The patient focus group identified no burdens associated with treatment. Some barriers to implementing VR interventions exist, including the need for a trained therapist, to be the voice for the avatar, and upfront costs, such as specialized equipment for VR interventions and equipment, which might sometimes be unavailable.(265)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(264-266) The Work Group's confidence in the quality of the evidence was very low. The confidence of the quality of evidence for multiple outcomes for both virtual reality interventions and avatar therapy was very low. The body of evidence had some limitations, including small sample sizes with inconsistent findings and noted biases.(264-266) The evidence base addressed minimal benefits of AT; however, several harms, burdens, or both, such as simulator sickness, which includes dizziness, nausea, headache, and eyestrain, were identified. Patient values and preferences varied because some patients might prefer other VR interventions as opposed to AT. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against virtual reality interventions, including avatar therapy, for individuals with schizophrenia.

Recommendation

36. We suggest using telephone-based care management to reduce rehospitalization days for individuals with schizophrenia.
    (Weak for | Reviewed, New-added)

Discussion

Telephone Intervention Problem Solving (TIPS) is a telenursing practice based on the theory of planned behavior and is conducted via weekly phone calls using problem solving. Information Technology Aided Relapse Prevention Programme in Schizophrenia (ITAREPS) is another weekly phone-based patient monitoring and disease management intervention for schizophrenia and other psychotic disorders to initiate early intervention of relapse (reoccurrence of previously treated psychotic symptoms) and to prevent hospitalizations.(267) Evidence suggests that the addition of telephone-based support to the treatment regimen of individuals with schizophrenia reduces rehospitalization occurrences.(267, 268)

An RCT (n=45) by Uslu et al. (2020) examining TIPS reported improvement in Medication Adherence Rating Scale (MARS) scores in two months.(269) However, another TIPS study by Beebe et al. (2017) with a larger sample size and limited generalizability (n=105) suggests no significant differences in pill-count adherence between groups at six months. However, a substantial improvement was noted in individuals' serum antipsychotic levels with an increased number of levels within the therapeutic range for a particular agent included in the study.(268)

An RCT (n=45) by Komatsu et al. (2013) revealed a significant reduction in rehospitalization days in the ITAREPS group compared with routine nursing care at 12 months but no difference in the number of relapses.(267) This same study found an improvement in the total symptom scores (using the BPRS) at relapse favoring ITAREPS, but no difference was evident at rehospitalization.

The overall findings of the limited evidence base included in the systematic evidence review covering telephone-based support suggest a reduction in rehospitalization days. Patient preferences regarding this treatment vary. The patient focus group noted individuals might not want to receive weekly calls from a health care provider or might find the intervention cumbersome, which could contribute to limited engagement. Further, consideration should be made for unhoused individuals or those with housing instability who might have inconsistent telephone access. Limitations, such as provider availability, could also impact service delivery.

Because this recommendation is categorized as *Reviewed, New-added*, the Work Group systematically reviewed evidence related to the recommendation.(267-269) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a small sample size and only one center in each study.(268) The benefits of telephone-based support in addition to TAU, including improved medication adherence and reduction in rehospitalization, outweighed the potential burden of receiving calls. Patient values and preferences varied because some patients preferred not to participate in a telemedicine intervention. Thus, the Work Group made the following recommendation: We suggest using telephone-based care management to reduce rehospitalization days for individuals with schizophrenia.

Recommendation

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)

Discussion

Shen et al. (2014) conducted an SR of 30 RCTs, 29 of which consisted of Chinese populations.(270) Evidence from only four of the RCTs indicated that acupuncture plus standard-dose antipsychotics improves positive and negative symptoms of schizophrenia compared with standard-dose antipsychotics alone in individuals with schizophrenia. The same four RCTs indicated that no such effect occurs in treatment with acupuncture plus low-dose antipsychotics.

Categories of acupuncture included in Shen et al. (2014) are traditional, electro-acupuncture, acupoint injection, laser acupuncture, and acupoint catgut embedding treatment. Low-quality evidence suggested that acupuncture added to antipsychotic medication might improve relapse rates and akathisia. Electro-acupuncture might decrease the likelihood that individuals will experience a worsening in global state.(270) Potential harm was noted in one study in the SR; low-quality evidence showed that electro-acupuncture could lead to various rates of spinal fracture among groups. None of the studies reported severe adverse outcomes, such as death, engagement with various services, patient satisfaction with care, QoL, or economic outcomes.(270)

Shen et al. (2014) suggests that acupuncture might have some antipsychotic effects, as measured on global and mental states, with few adverse effects.(270) Many categories of acupuncture might be relatively safe, with few adverse effects, accessible and inexpensive in China, and widely used to treat psychotic symptoms. However, larger, more well-designed studies that add sham conditions, blinding, or both are needed. Currently, the evidence is indirect and has limited generalizability because most of the studies were conducted in a setting in which acupuncture is an accepted modality of traditional medicine. However, given the promising applicability, additional research should be conducted in other contexts.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(270) The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including cultural factors that might impact the generalizability to individuals in the VA and DoD settings. Further, acupuncture might be less readily available within DoD, and patients in both VA and DoD might or might not be comfortable with acupuncture as a treatment modality. Cultural differences might also impact patients who are open to or who prefer this type of treatment. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against

augmenting pharmacotherapy with acupuncture to reduce negative and positive symptoms for individuals with schizophrenia.

Recommendation

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)

Discussion

The overall morbidity and mortality in patients with schizophrenia when compared with the general population is striking. It is estimated that on average, individuals with schizophrenia in the U.S. die 28.5 years earlier than those without schizophrenia.(271)

The original goal of the Work Group was to evaluate whether collaborative, team-based models, systematic monitoring, and patient engagement strategies improved outcomes related to health promotion, primary, secondary, and tertiary disease prevention in addition to co-occurring general health conditions in this population. Unfortunately, no studies that addressed collaborative care, interdisciplinary treatment approaches, systematic monitoring, or patient reminder systems and that met the search criteria were identified. In addition, the studies available that looked at educational programs for lifestyle interventions for blood pressure, cholesterol, and self-management education for medical adherence showed no improvement when compared with TAU.(219, 272) More high-quality studies are needed to adequately address this area of interest. The evidence reviewed suggests the use of case management in individuals with schizophrenia improves colon cancer and lung cancer screening rates compared with TAU.(273) Fijiwara et al. (2021) conducted a small RCT (n=127) that evaluated colon cancer screening in patients with schizophrenia and showed improved participation in colon cancer screening with case management versus TAU. In this study, the primary goal and, thus, the majority of most of the case management intervention, was directed toward colon cancer screening. The case management also provided patients with information regarding other preventive screenings, including lung cancer, gastric cancer, breast cancer, and cervical cancer. The secondary outcomes in the study were mixed but showed that lung cancer screening improved with case management. However, gastric, breast, and cervical cancer screening rates showed no significant difference with case management compared with TAU.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(219, 272, 273) The Work Group's confidence in the quality of evidence is low. The body of evidence has some significant limitations, including a single small RCT, a Japanese patient population ungeneralizable to the U.S. population, a single primary outcome of colon cancer screening, and a lack of secondary or tertiary prevention studies. There was a lack of meaningful evidence justifying the use of case management to improve medical outcomes or preventive

screening. There was insufficient evidence to determine the balance of benefits and harms. Thus, the Work Group made the following recommendation: There is insufficient evidence to suggest case management to improve preventive screening and/or medical outcomes for individuals with schizophrenia.

Recommendation

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)**

Discussion

That individuals with SMI, including schizophrenia, smoke tobacco at higher rates and have an increased incidence of smoking-related morbidity and mortality when compared with the general population has been well established. It is estimated that tobacco use in individuals with schizophrenia is approximately 5.3 times higher than the average population (not included in the evidence base nor impacting the strength of this recommendation).(274) However, little information is available regarding which types of interventions are most effective in this population. In addition, the current systematic evidence review did not identify studies about the effectiveness and safety of pharmacotherapy for tobacco use disorders in this population. Individualized intervention is specifically tailored to the patient. In the case of individuals with schizophrenia, interventions should target issues specific to this population, including

- Higher levels of nicotine addiction (275, 276),
- SMI symptoms of schizophrenia (275),
- Side effects of antipsychotic medications (275), and
- Concerns that quitting tobacco limits coping strategies (275).

An SR by Spanakis et al. (2021) identified three RCTs (n=921) that found improved rates of tobacco cessation with individualized face-to-face interventions when compared with TAU.(275)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(275, 276) The Work Group's confidence in the quality of the evidence for individualized tobacco cessation was moderate. The body of evidence had some limitations, including the non-standardization of this intervention. Given the large number of patients with schizophrenia and concurrent tobacco use, a standardized way of delivering tobacco cessation intervention specific to this population is important. Another limitation was the lack of conclusive data on individualized interventions delivered online or digitally. This is because the studies included in the SR were insufficiently powered to detect a statistically significant difference between individualized machine-based interventions versus generic machine-based interventions because of the small sample sizes. Given the increase in patients

receiving care virtually, more research is needed to determine whether a tobacco cessation intervention specifically tailored for patients with schizophrenia is effective in settings outside traditional face-to-face care. The benefits of customized face-to-face tobacco cessation interventions outweigh the harms. Patient preferences varied somewhat because some patients might be uninterested in tobacco cessation or face-to-face interventions. In addition, concern exists that the intervention is time and resource intensive. Thus, given the evidence supporting this intervention and the minimal risk of harm, the Work Group made the following recommendation: We recommend a face-to-face individualized smoking cessation intervention tailored specifically to the patient for individuals with schizophrenia.

Recommendation

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)

Discussion

The use of dietary interventions, exercise, individual lifestyle counseling, psychoeducation for weight reduction, or a combination of the foregoing for individuals with schizophrenia has been demonstrated to have low to moderate effectiveness.(148) These interventions should be considered in treatment planning in parallel with the pharmacologic strategies discussed in Recommendation 15. In this recommendation, the evidence shows that non-pharmacologic treatments demonstrated variations in weight reduction outcomes depending on the treatment selected. Meta-analytic data was considered and reviewed for multiple non-pharmacologic interventions. These interventions include, but are not limited to, individual and group lifestyle counseling, psychoeducation, exercise, and dietary interventions.(148) When considering treatments, such as individualized lifestyle counseling and exercise, outcomes demonstrated large weight-reducing effects, whereas cognitive behavioral interventions and psychoeducation demonstrated small and medium weight-reducing effects.

Weight gain (which can be a symptom of metabolic dysfunction), obesity, and resultant medical problems are recognized as critical side effects and pervasive problems in schizophrenia. Many medications prescribed for schizophrenia cause substantial weight gain, and obesity has damaging health consequences, including cardiovascular morbidity, diabetes, and reduced life expectancy. Evidence suggests that the use of a chronic care model (e.g., Enhancing Quality of Care in Psychosis [EQUIP]) increases the use of weight services and improves weight outcomes in schizophrenia.(276) EQUIP was tested in an eight-site clustered controlled implementation trial (n=801).(276) The intervention included patient-facing kiosks placed in clinic waiting

rooms. The kiosks included a touchscreen monitor, computer, headphones, printer, and scale, and patients entered their weight at every clinic visit. Kiosk data were automatically reported to providers and care managers to identify potential referrals to weight services, and overweight patients received talking points to help them advocate for a referral to a wellness program and a change of medication to one with lower weight gain liability. EQUIP included the implementation of a group-based weight management program that took into account the cognitive deficits often present in individuals with schizophrenia. It also used an evidence-based quality improvement framework that included multidisciplinary quality improvement teams, continuous feedback to staff, and provider and patient education.

Similar interventions are also discussed in Recommendation 30, where aerobic exercise is specifically addressed as an intervention to reduce symptoms as well as to provide overall health benefits.

Vancampfort et al. (2019) conducted a meta-review of six meta-analyses that systemically and quantitatively analogized non-pharmacologic interventions.(148) These meta-analyses evaluated interventions, non-pharmacologic interventions, non-pharmacologic interventions' nature, and their effects on body weight among individuals treated for schizophrenia. The most effective intervention was noted to be individual lifestyle counseling, followed by exercise alone when seeking a desired outcome of body weight reduction.(148)

Young et al. (2019) found that individuals in sites assigned to the EQUIP intervention (n=389) were 2.3 times more likely to use weight services compared with those at control sites (n=412), and individuals' final weight at control sites was 5.9 ± 2.7 kg heavier than at intervention sites.(276) The Work Group determined that the benefits of a chronic care model for schizophrenia outweighed the harms and burdens, which were minimal. The requirement to attend wellness groups can be burdensome to some. However, the adverse outcomes of not monitoring and managing weight can be potentially severe.

Evidence suggests that patients benefit from other health advantages, such as a decrease in waist circumference, BMI, blood pressure, and glucose levels, with these interventions. Other factors the Work Group considered were the variations in patient values and preferences. Some patients might have difficulty making the recommended behavior and lifestyle modifications. Culture (e.g., related to food, diet) might also affect the acceptability of some non-pharmacologic interventions. Other implications the Work Group discussed were resource use and equity. For instance, providers might need specialized skillsets, such as dietetics, and training in weight stigma and eating disorders. Subgroups of people who might live in food deserts, limiting access to a wide variety of food choices, or have limited means to access a wide variety of food choices should also be considered. Of note, research on the relationship between weight and health is complicated, with studies showing that exercise and other positive health

behaviors can improve health without depending on weight loss. Rehabilitation, health coaching, exercise, and movement specialists having the necessary competency and skillset working with mental health diagnoses should be consulted for addressing functional and wellness needs and provision of appropriate supportive services.

In addition, patient preferences varied regarding different aspects of the EQUIP intervention. Patients were supportive of the automated collection of outcomes data and thought their providers found the data useful. They also reported satisfaction with the weight management program and particularly liked sharing their experiences with one another, learning to cook, and having opportunities to exercise. However, many did not engage with the program because they did not want to be in a group intervention, did not think weight services were needed, lacked transportation or were too far from the clinic, were unaware of the availability of such services, or were too symptomatic to attend or to engage in group therapy.

Implementation of the kiosks and software to capture weight might be infeasible at sites with inadequate funding or space. If kiosks are unavailable, it is unclear who would be responsible for weighing patients and how that data would be communicated to the appropriate providers who could act on it. Implementation of the weight management program developed by the EQUIP team also requires staff to run the groups and to train others in delivering the intervention.

Although the primary outcomes in the EQUIP study were weight and BMI, it is widely understood that other metabolic factors, such as fasting glucose, blood pressure, cholesterol, triglycerides, and waist circumference, are important to monitor and manage. The American Psychiatric Association Schizophrenia Treatment Guidelines (2021) make suggestions for physical and laboratory assessments that should be conducted at baseline and follow-up.(277)

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(148, 276) The Work Group's confidence in the quality of evidence was low. It was found in the study discussed by Young et al. (2019) that the body of evidence had some limitations, including a lack of blinding and an unequal rate of attrition between groups (21.5% in the intervention group and 13.3% in the control group).(276) The benefits of the use of non-pharmacologic interventions, such as dietary interventions, exercise, and psychoeducation for weight loss outweighed the harms and burdens of use. The benefits of using a chronic care model to increase the use of weight management services and to improve weight outcomes outweighed the potential harms. Patient values and preferences varied because some patients did not want to engage in a weight management program, although others were satisfied with it. There was concern regarding some patients' ability to exercise based on environment, co-occurring conditions, or both. It is also important to highlight that although the interventions were studied individually, they can be used together. Thus, the Work Group made the

following recommendation: 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.

Recommendation

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)

Discussion

In some populations, more than 50% of individuals with SMI are diagnosed with co-occurring substance use disorder.(278) Several known psychosocial interventions are used to treat this population, but little guidance is available regarding which modality works best. In an SR of 32 studies (n=3,165), Hunt et al. (2019) evaluated several psychosocial interventions, including CBT, CBTp motivational interviewing, contingency management, integrated models of care, motivational interviewing, non-integrated models of care (i.e., intensive case management), and skills training.(278)

Based on the evidence identified, no overall difference in the outcomes related to substance use or symptoms occurred with any of the above interventions when compared with TAU.(278) In addition, these interventions were not found to show improvement in other outcomes, including function, adherence, QoL and wellbeing, and self-harm when compared with TAU.

Although one study found adherence favored TAU when compared with skills training, some studies within the SR showed benefits for certain interventions, including the following.(278)

- *CBT plus motivational interviewing versus TAU* – One study (n=110) found improved general life satisfaction scores at six months (better QoL).
- *Contingency management versus TAU* – One study (n=176) found decreased hospitalization at six months.
- *Motivational interviewing versus TAU* – One study (n=28) found a benefit from motivational interviewing in improving alcohol abstinence at six months.
- *Non-integrated models of care (intensive case management) versus TAU* – One study (n=29) found improved functioning using global scores (RFS).
- *Skills training versus TAU* – One study (n=47) found improved adherence with TAU.

Despite these findings, overall, the data shows a lack of evidence to support one intervention over another.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(278) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had several limitations, including high attrition rates, inconsistent outcome measures, settings, and small sample sizes. There was insufficient evidence to determine the balance of benefits and harms. Patient values and preferences varied because most patients do not typically express a preferred psychosocial intervention. Further, there are concerns regarding equitable access to the interventions because psychosocial treatments are resource intensive, might be unavailable in some facilities, and often require specialized training. Thus, the Work Group made the following recommendation: 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.

X. Research Priorities

During the development of the 2023 Schizophrenia CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs. In addition, the Work Group recognized the need to complement these recommendations with participatory action research that would engage individuals with schizophrenia and their families in reviewing these guidelines, identifying gaps in the recommendations and in current care as well as in dialog to translate recognition of gaps into areas for research.

In reviewing the available evidence and using it to formulate recommendations or suggestions, the Work Group raised a substantial number of questions that could not be answered with the available evidence. These questions concerned the following.

- Characterizing individuals
    - What genomic, neuroimaging, cognitive, and behavioral markers can support the diagnosis and identification of treatment- or outcome-relevant subtypes of schizophrenia for individuals experiencing first episodes and others?
- Characterizing clinical status and the outcomes of care
    - Most significantly, what measures can be used to provide measurement-based care for individuals with schizophrenia?
    - What measures can guide the identification of needs, treatment planning, and assessment of treatment outcomes?

- How should measures of symptoms be supplemented with measures of cognition, functioning, QoL, treatment adherence, recovery, and the experience of both illness and the care received?
- What patient-reported outcome measures are valid and reliable in individuals with schizophrenia? For example, can symptoms be accurately assessed using patient-reported outcome measures, or should patient-reported measures focus on other domains, such as comorbid disorders, functioning, and QoL?
- For what measures has the sensitivity to change been evaluated, and what represents clinically meaningful change?
- What is the appropriate frequency for repeat administrations to maximize treatment outcomes?
- Should inputs into decision making include patient-reported outcomes and provider ratings as well as reports from significant others, physiological measures, output from devices (e.g., pill dispensers, activity monitors), input from experience sampling, and other modalities?
- What methods can be used for data acquisition that minimize burdens for both patients and providers?
- Can predictive modelling identify individuals with schizophrenia (first episode and others) at increased risk for suicide, overdose, external cause mortality, and excess all-cause mortality, and support targeting of those at high risk with interventions to prevent these outcomes?

- Treatment of first episodes
  - What is the duration of early intervention services needed to optimize long-term outcomes for individuals with first-episode psychosis?
  - How should families be included in care?
  - How can early intervention services be implemented for active-duty Service members with first-episode psychosis as they are preparing for medical discharge?
  - What is the prevalence of first-episode psychosis in Service members who receive an Entry Level Separation?
  - How can VA's Early Psychosis Intervention Coordination Program be implemented to achieve the greatest alignment with the package of services included in the Coordinated Specialty Care model for the greatest number of individuals with first episode psychoses?
- Pharmacologic and other somatic treatments
  - What genomic, neuroimaging, cognitive, behavioral, and other markers predict responses to specific medications?

- Are there other medications effective for negative symptoms and cognitive impairments?
- When is augmenting or switching antipsychotic medications appropriate?
- What treatments are most effective for individuals with clozapine-resistant schizophrenia?
- How can adherence to oral medications be monitored most reliably? What interventions can improve adherence to treatment with antipsychotic medications?
- What neuromodulatory interventions are effective for what outcomes and with what stimulation parameters?
- What is the duration of responses for each neuromodulatory intervention, and what can be done to maintain gains?
- What are the adverse effects of anticholinergic medications on oral health, and what can be done to prevent them?
- Is vitamin B6 or vitex agnus castus effective for addressing prolactin-related adverse effects of antipsychotic medications in women?
- Can the use of point-of-care administration of required blood tests increase clozapine prescribing?

- Psychotherapy, psychiatric rehabilitation, and other psychosocial treatments
  - Because most studies of psychosocial treatments that support functioning, community integration, and other non-symptom outcomes have broad diagnostic inclusion criteria, rather than a singular focus on individuals with schizophrenia, how important is conducting randomized controlled trials of psychosocial interventions on specific diagnostic subgroups? Or is it possible to generalize the effects of these treatments to individuals with schizophrenia? How important are diagnosis-specific Clinical Practice Guidelines when recommending psychosocial interventions?
  - Should early intervention services (e.g., an integrated, comprehensive package of treatments) be viewed as a model for care for all people with schizophrenia?
  - What characteristics predict responses to specific psychotherapies (e.g., CBT, CBTp, metacognitive therapy, positive psychology)? Which treatments are indicated (e.g., booster sessions versus other therapies) if gains from psychotherapy are lost?
  - Are behavioral health advance directives effective for preventing dropouts from care, suicidal behavior and other forms of self-harm, and involuntary hospitalization for individuals with schizophrenia?

    - How should psychosocial and rehabilitative strategies be combined or sequenced to improve symptoms, functioning, and QoL? For example, what is the effectiveness of ACT combined with cognitive remediation? How can current Individual Placement and Support models for vocational rehabilitation be enhanced? What interventions for which individuals with schizophrenia are effective when they are delivered by peer providers?
    - What interventions are effective by themselves, in combination, or in sequence for improving symptoms, QoL, and functioning in individuals with coexisting schizophrenia and posttraumatic stress disorder?
    - Can skills training or other rehabilitation strategies be effective for improving parenting for individuals with schizophrenia who have children?
    - What psychotherapies or psychosocial interventions are effective for preventing suicidal behavior or other forms of self-harm for individuals with first episode psychoses or schizophrenia?
    - When should intensive models of support (ACT, supported employment) be tapered or discontinued?
    - How should psychosocial treatments be coordinated over time with pharmacologic treatment? Should they be intensified for individuals with antipsychotic treatment-resistant schizophrenia or individuals with clozapine-resistant schizophrenia?
- Minimizing or discontinuing antipsychotic medication
    - What percentage of individuals with schizophrenia wish to minimize, decline, or discontinue antipsychotic medication, and why?
    - Are there strategies to successfully support individuals who wish to decline pharmacologic interventions or to minimize the medication they take through psychosocial interventions?
    - Do current models (e.g., Cooper et al. [2020]) (279) hold promise, must new interventions be developed, or both?
    - Are there unique characteristics that predict which individuals with schizophrenia might be successfully maintained with no or minimal antipsychotic medication?
- Crisis services
    - What are effective alternatives to acute psychiatric treatment, restrictive crisis care, or both? For example, are peer respite models effective and scalable? How can individuals with schizophrenia experiencing relapse be supported in the least restrictive environments possible? What system changes are necessary to support individuals' autonomy while in crisis?

    - How can the health system work effectively with crisis responders (law enforcement, first responders) to prevent unnecessary trauma to individuals in crisis?
- Whole Health
    - How should the principles of Whole Health inform care for people with schizophrenia?
    - Which of the following movement and exercise therapies—yoga, tai chi, and qigong—are most effective for people with schizophrenia? Is acupuncture effective? For what outcomes? For whom?
- General health care
    - What strategies for care delivery are most effective for managing the adverse effects of antipsychotic medications?
    - Are there strategies for primary and preventive health care that can decrease the excess mortality observed in people with schizophrenia?
- Social determinants of health
    - Are there racial and ethnic disparities in the diagnosis of schizophrenia, the availability of evidence-based treatments, and the outcomes of care?
    - Are there interventions that can mitigate the impact of the negative associations between schizophrenia and social determinants of health, such as discrimination, isolation, poverty, and exposure to violence?
    - Are individuals with schizophrenia less likely to have access to needed technological resources and digital access to support their care? Are there subgroups who are less likely than others to have access to digital technologies? How could access be improved?
- Schizophrenia and aging
    - What models of care provide the best outcomes for integrating physical and mental health care for older adults with schizophrenia?
    - Is long-term exposure to anticholinergic medication a risk factor for late-life dementia in individuals with schizophrenia?
    - How can data from cross-sectional and longitudinal studies of aging in people with schizophrenia, including data related to biomarkers, inform interventions to increase health, cognition, and functioning in individuals with schizophrenia as they age?
    - What treatments are safe and effective for schizophrenia in late life?
    - What training or other resources are needed to overcome barriers related to community resources and options for housing and care for older individuals with schizophrenia? What training or other resources are

needed to ensure that staff in nursing homes and other forms of senior housing understand the needs, motivations, and symptoms of residents with schizophrenia?

Addressing some of these questions will require highly innovative research likely to be competitive for research funding. However, many of the questions are critically important but unlikely to be considered innovative, such as those about durations of treatment, when treatments should be continued, when they should be augmented, when they should be switched, and about how the treatment should be sequenced when switches are appropriate. The answers to these questions are needed to improve care, but the answers are less likely to come from research funded and implemented through competitive processes.

The magnitude of the questions that must be addressed to improve these guidelines, together with limitations in the number of studies that could reasonably be implemented through current funding mechanisms, might require novel strategies for advancing knowledge that could be based on quality improvement and program evaluation as well as on research within the VA/DoD. An early step might be to support the development of measures and methods to be used in measurement-based care for schizophrenia. A better understanding of how to implement measurement-based care in schizophrenia to improve clinical care appears to be a sound first step. When there is sufficient uptake by providers within the health care system to support it, outcome measures could then be examined for quality improvement purposes, as well as research. Establishing system-wide use of measurement-based care could then facilitate studies on interventions. Another next step might be to develop an infrastructure that would support an array of simple, pragmatic, point-of-care randomized clinical trials for alternative interventions where equipoise exists between benefits and risks as a component of quality improvement.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 20 key questions (KQ) on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 lists and describes the PICOTS elements.

Table A-1. PICOTS (280)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition or conditions, populations or sub-populations, disease severity or stage, co-occurring conditions and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic or screening test or both used with the patient or population.
Comparator	Treatment or treatments (e.g., placebo, different drugs) or approach or approaches (e.g., different dose, different frequency, standard of care) being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if Applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if Applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or a type of practice.

Abbreviations: PICOTS: population, intervention, comparison, outcome, timing, and setting

Because of resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 20 highest priority KQs for inclusion (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1–9 scale (7–9, critical for decision making; 4–6, important, but not critical, for decision making; and 1–3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Populations

- Key Questions 1–17
    - Including: Adults with schizophrenia, schizophrenia spectrum disorders, schizoaffective disorder, schizophreniform symptoms, first-episode

psychosis, first-episode schizophrenia, or schizophrenia with catatonia, being treated in any setting
    - Excluding: Pregnant people
- Key Question 17
    - Including: A subset of the standard population with cognitive impairments, negative symptoms (i.e., blunted affect, poverty of speech, anhedonia, asociality, amotivation), or both
    - Excluding: Pregnant people

b. Interventions

- Key Question 1
    - Prodromal tools
        - Prodromal Questionnaire brief (PQ-B)
        - PRIME screen
    - Assessment tools, approaches, or both
        - SCID-P
        - MINI
    - Biomarkers
        - Genetic (GWAS data, specific genes [MTHFR, COMT 675A and FOLH1])
        - Imaging (PET, MRI, fMRI)
        - Endocrine (Cortisol, thyroid, melatonin, others)
        - EEG (different modalities)
        - Serum B12 and folate levels
- Key Question 2
    - Symptoms
        - BPRS
        - PANNS
        - BASIS
        - MCSI
        - ReQoL
        - MIRECC GAF (symptom scale)
    - Medication adherence
        - Medication possession ratio (MPR)

        - Gap measure
        - Microelectronic monitoring system
        - Blood or urine tests or both
    - Medication side effects
        - BMI
        - Fasting glucose or HgA1c
        - Lipids
        - Bun/creatine – renal function
        - WBC – leukopenia
        - Blood pressure
        - LUNERS
        - Arizona Sexual Experience Scale (ASEX)
    - Drug or alcohol use or both
        - Brief Addiction Monitor (BAM)
        - Need to identify other outcome measurement tools for alcohol use and drug use
    - Functioning
        - MIRECC GAF (social and work scales)
        - WHODAS 2.0
        - QoL Interview
        - Social Attainment Scale (SAS-II)
        - Indiana Job Satisfaction Scale
    - Sleep
        - Epworth Sleepiness Scale
- Key Question 3
    - Models of medical care, care systems, or both
        - Patient-Centered Medical Home (PCMH)
        - CSC
        - Individualized case management services
        - Enhancing Quality of Care in Psychosis (EQUIP)
        - Whole health approach
        - Health coaching

- Key Question 4
  - CSC
  - NAVIGATE
  - OnTrackNY
  - Specialized Treatment Early in Psychosis (STEP) program
  - Early Assessment and Support Alliance (EASA)
  - Connection Program
- Key Question 5
  - First- and second-generation antipsychotic medication
    - Aripiprazole LAI
    - Aripiprazole Lauroxil
    - Aripiprazole Monohydrate
    - Asenapine
    - Brexipiprazole
    - Cariprazine
    - Chlorpromazine
    - Clozapine
    - Fluphenazine decanote
    - Fluphenazine LAI
    - Haloperidol decanoate
    - Haloperidol LAI
    - Iloperidone
    - Loxapine
    - Lumateperone
    - Lurasidone
    - Molindone
    - Olanzapine pamoate (olanzapine LAI)
    - Paliperidone Palmitate
    - Paliperidone LAI
    - Perphenazine
    - Quetiapine
    - Risperidone

        - Risperidone LAI
        - Thiothixene
        - Thioridazine
        - Trifluoperazine
        - Ziprasidone
- Key Question 6
    - Antipsychotic medications or medications, either as monotherapy or in combination
- Key Question 7
    - Pharmacotherapy, including
        - Benztropine
        - Diphenhydramine
        - Trihexyphenidyl
        - Benzodiazepines
        - Amantadine
        - Propranolol
        - VMAT2 inhibitors
        - Vitamin E
        - Levetiracetam
        - Branch chained amino acids (BCAA)
        - Pyridoxine
        - Clozapine
        - Metformin
        - Topiramate
        - Change dose of medication, wellness programs (can include elements of weight loss, exercise, sleep hygiene), or both
        - VA MOVE program
        - Lifestyle interventions
- Key Question 8
    - Neuromodulatory and somatic therapies, including
        - Deep brain stimulation (DBS)
        - Electro-convulsive therapy (ECT)
        - Transcranial magnetic stimulation (TMS)

    - Vagus nerve stimulation (VNS)
- Key Question 9
    - Long-acting injectable medications
    - Orally disintegrating tablets with supervision
    - Education about side effects
    - Motivational interviewing
    - Shared decision making
    - Court-ordered treatment
    - Pill boxes
    - Blister packs
    - Electronic devices
- Key Question 10
    - Cognitive behavioral therapy (including variants such as CBTp)
    - Metacognitive training, therapy, or both
    - Acceptance and commitment therapy
    - Positive psychotherapies (e.g., WELLFOCUS)
    - Skills training (e.g., social skills training)
    - Illness Management and Recovery
    - Individual Resiliency Training
    - Art therapies
- Key Question 11
    - Combination pharmacotherapy and psychotherapy
- Key Question 12
    - Caregiver support programs
    - Family psychoeducation
    - Veteran-Centered Brief Family Consultation
    - Behavioral Family Therapy
    - Integrative Behavioral Couples Therapy
    - Multifamily Group Therapy
- Key Question 13
    - Mutual support interventions (e.g., Intentional Peer Support, Vet-to-Vet)
    - Peer specialists or peer providers in mental health services

    - Self-help groups, including 12-step groups (e.g., Recovery International)
    - Peer run respite
- Key Question 14
    - Intensive case management
    - Assertive Community Treatment
    - Strengths Case Management
    - Integrated Dual-Diagnosis Treatment
    - Mental Health Intensive Case Management, RANGE, and eRANGE (VA-specific models)
    - Supported housing (e.g., Housing First, congregate housing, group housing)
    - Assertive Community Treatment or MHICM
- Key Question 15
    - Supported employment (e.g., IPS)
    - Transitional work
    - Pre-vocational training, volunteering, Clubhouse, etc.
- Key Question 16
    - Usual care, plus
        - Structured relaxation techniques
        - Meditation
        - Stress management
        - Yoga, tai chi, or other body movement work
        - Acupuncture
        - Mindfulness practice or mindfulness-based stress reduction
- Key Question 17
    - Pharmacotherapy
        - N-acetyl-cysteine
        - Galantamine
        - Oxytocin
        - Tropisetron
        - Memantine eltoprazine
        - Cycloserine
        - N-methyl-d-aspartate glutamate receptor (NMDAR) enhancers

        - Raloxifene
        - Newer antipsychotics (SGA), including
            - aripiprazole
            - asenapine
            - lurasidone
            - paliperidone
            - ziprasidone
    - Non-pharmacologic therapies
        - Neuromodulation (rTMS and tDCS)
        - Cognitive rehabilitation
        - Cognitive remediation
        - Cognitive enhancement
        - Combined approaches
        - Exercise
- Key Question 18
    - Collaborative care
    - Integrated health care system, medical case management
    - Interdisciplinary treatment approach
    - Systematic monitoring
    - Supported self-management
    - Patient reminder systems
    - Interactive patient health records
    - Coordination of smoking cessation and lifestyle interventions to prevent cardiovascular disease with mental health care
    - Peer support focused on overall health
- Key Question 19
    - Programs for care delivery
        - Collaborative care
        - Integrated health care system
        - Medical case management
        - Interdisciplinary treatment approach
        - Systematic monitoring

        - Supported self-management
        - Patient reminder systems
        - Interactive patient health records
- Key Question 20
    - Synchronous or asynchronous
        - Video call interventions
        - Telephone interventions
        - Hybrid telehealth and in-person visits
        - Apps or technological approaches (without clinical monitoring)
        - Mobile apps, including apps related to sleep
        - Computer or web-based interventions
        - Automated or computer-based restorative, neuroplasticity-based cognitive remediation, cognitive therapy, cognitive rehabilitation

c. Comparators

- Key Question 1
    - Other assessment tools, approaches, or biomarkers (including standard clinical assessment)
    - Clinical interview
- Key Question 2
    - Usual care
    - Other types of measurement approach (e.g., self-report versus provider-administered or administrative data)
- Key Question 3
    - Usual care
    - Other models of care
- Key Question 4
    - Usual care
    - Other models of care
- Key Question 5
    - Placebo
    - Other dose or duration of the same pharmacotherapy or both

- Key Question 6
  - One of the following
    - Placebo
    - Other antipsychotics
    - Monotherapy versus combination therapy
- Key Question 7
  - Other pharmacotherapy or no pharmacotherapy
- Key Question 8
  - One of the following
    - Sham treatments
    - Pharmacotherapy
    - Combinations
- Key Question 9
  - Usual care
- Key Question 10
  - No psychotherapy (active comparator)
  - Different psychotherapy
- Key Question 11
  - Pharmacotherapies (listed above) or psychotherapy monotherapy
- Key Question 12
  - TAU/No psychoeducation
  - Family psychoeducation
- Key Question 13
  - TAU/No peer services
- Key Question 14
  - TAU
- Key Question 15
  - TAU
  - Another vocational rehabilitation model
- Key Question 16
  - TAU, plus
    - Placebo or sham intervention or both (if appropriate)

        - Active control
- Key Question 17
    - Other listed interventions
    - First-generation antipsychotics
    - Placebo or TAU
- Key Question 18
    - TAU
- Key Question 19
    - TAU
- Key Question 20
    - TAU, with or without professional peer-support or coaching
    - Other technology-based intervention

d. Outcomes

- Key Question 1
    - Critical outcomes
        - Diagnostic accuracy, sensitivity, or both
- Key Question 2
    - Critical outcomes
        - Symptom reduction or remission
        - Functional status: vocational, educational, or both; social
    - Important outcomes
        - Reduction in self-harm (including suicide)
        - QoL, wellbeing, and recovery
        - Treatment adherence
        - Relapse, recurrence, and hospitalization
        - Medication-related adverse events, including serious adverse events, metabolic symptoms, and cardiac events (specifically QTc prolongation)
- Key Question 3
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms

    - Important outcomes
        - Reduction in self-harm
        - Functional status: vocational, educational, or both; social
        - Treatment adherence
        - Relapse, recurrence, and hospitalization
        - Medication-related adverse events, including serious adverse events, metabolic symptoms, and cardiac events (specifically QTc) prolongation)
        - Impact on family
- Key Question 4
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Functional status: vocational or educational or both; social
    - Important outcomes
        - Reduction in self-harm (including suicide)
        - QoL, wellbeing, and recovery
        - Treatment adherence
        - Relapse, recurrence, and hospitalization
        - Impact on family
- Key Question 5
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Relapse, hospitalization, or both
        - Medication-related adverse events, including serious adverse events, metabolic symptoms, and cardiac events (specifically QTc prolongation)
        - QoL, wellbeing, recovery
        - Functional status: vocational, educational, or both; social
    - Important outcomes
        - Reduction in self-harm (including suicide)

- Key Question 6
  - Critical outcomes
    - Symptom reduction or remission: positive, secondary outcomes of negative and cognitive symptoms
    - Medication-related adverse events, including serious adverse events, metabolic symptoms, and cardiac events (specifically QTc prolongation)
    - Relapse, recurrence, and hospitalization
    - Treatment adherence
  - Important outcomes
    - Reduction in self-harm (including suicide)
    - QoL, wellbeing, recovery
    - Functional status: vocational, educational, or both; social
- Key Question 7
  - Critical outcomes
    - Change in symptoms based on standard tests or rating scales (Barnes, Simpson-Angus, AIMS, DISCUS)
    - Medication-related adverse events, including serious adverse events, metabolic symptoms, and cardiac events (specifically QTc prolongation)
  - Important outcomes
    - QoL, wellbeing, recovery
    - Treatment discontinuation (for any reason), including by provider
    - Treatment adherence
- Key Question 8
  - Critical outcomes
    - Symptom reduction or remission: positive, negative, and cognitive symptoms
  - Important outcomes
    - Serious adverse events, including metabolic symptoms and cardiac events
    - Reduction in self-harm (including suicide)
    - QoL, wellbeing, and recovery
    - Functional status: vocational, educational, or both; social

        - Relapse, recurrence, and hospitalization
        - Treatment adherence
- Key Question 9
    - Critical outcomes
        - Treatment adherence
    - Important outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - QoL, wellbeing, and recovery
        - Functional status: vocational, educational, or both; social
        - Treatment discontinuation (for any reason), including by provider
        - Reduction in self-harm (including suicide)
        - Relapse, recurrence, and hospitalization
- Key Question 10
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Functional status: vocational, educational or both; social
    - Important outcomes
        - QoL, wellbeing, and recovery
        - Reduction in self-harm
        - Relapse, recurrence, and hospitalization
        - Treatment adherence
        - Treatment discontinuation (for any reason), including by provider
- Key Question 11
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Reduction in self-harm (including suicide)
        - Serious adverse events, including metabolic symptoms and cardiac events
    - Important outcomes
        - QoL, wellbeing, and recovery

        - Functional status: vocational, educational, or both; social
        - Relapse, recurrence, and hospitalization
        - Treatment adherence
- Key Question 12
    - Critical outcomes
        - Impact on family
        - Relapse, recurrence, or hospitalization
    - Important outcomes
        - QoL, wellbeing, and recovery
        - Functional status: vocational, educational, or both; social
        - Reduction in self-harm
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Treatment adherence
- Key Question 13
    - Critical outcomes
        - Treatment adherence
    - Important outcomes
        - QoL, wellbeing, and recovery
        - Functional status: vocational, educational, or both; social
        - Relapse, recurrence, and hospitalization
        - Reduction in self-harm (including suicide)
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Exercise and nutrition
- Key Question 14
    - Critical outcomes
        - Housing, housing stability, and homelessness
        - Relapse, recurrence, and hospitalization
    - Important outcomes
        - Functional status: vocational, educational, or both; social
        - QoL, wellbeing, and recovery
        - Reduction in self-harm (including suicide)

        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Treatment adherence
- Key Question 15
    - Critical outcomes
        - Work domains and employment
        - Functional status: vocational, educational, or both; social
    - Important outcomes
        - QoL, wellbeing, and recovery
        - Reduction in self-harm (including suicide)
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
        - Relapse, recurrence, and hospitalization
        - Treatment adherence
- Key Question 16
    - Critical outcomes
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
    - Important outcomes
        - Reduction in self-harm (including suicide)
        - QoL, wellbeing, and recovery
        - Functional status: vocational, educational, or both; social
        - Relapse, recurrence, and hospitalization
        - Anxiety and stress
        - Treatment adherence
- Key Question 17
    - Critical outcomes
        - Cognitive impairments
            - Nonsocial (processing speed, verbal memory, visuospatial memory, working memory, attention, reasoning, and problem solving)
            - Social (emotion processing, social perception bias, attribution, mentalizing, facial recognition, auditory recognition, processing, or both)

            - Negative symptoms, including composite measures (blunted affect, poverty of speech, anhedonia, asociality, amotivation)
        - Negative symptom subfactors: emotional expression and avolition or asociality
        - Functional status (vocational, educational, social, community)
    - Important outcomes
        - Treatment adherence and discontinuation
        - Relapse, recurrence, and hospitalization
        - Serious adverse events, including metabolic symptoms and cardiac events
- Key Question 18
    - Critical outcomes
        - Increased uptake of primary, secondary, and tertiary disease prevention (e.g., prevention guidelines adherence, including immunizations, giving up or not starting smoking, routine screenings [cervical and breast cancer]) as well as early treatment and adherence
        - Morbidity
    - Important outcomes
        - Morality
- Key Question 19
    - Critical outcomes
        - Substance use
        - Symptom reduction or remission: positive, negative, and cognitive symptoms
    - Important outcomes
        - Reduction in self-harm (including suicide)
        - QoL, wellbeing, and recovery
        - Relapse, recurrence, and hospitalization
        - Functional status: vocational, educational, or both; social
        - Treatment adherence

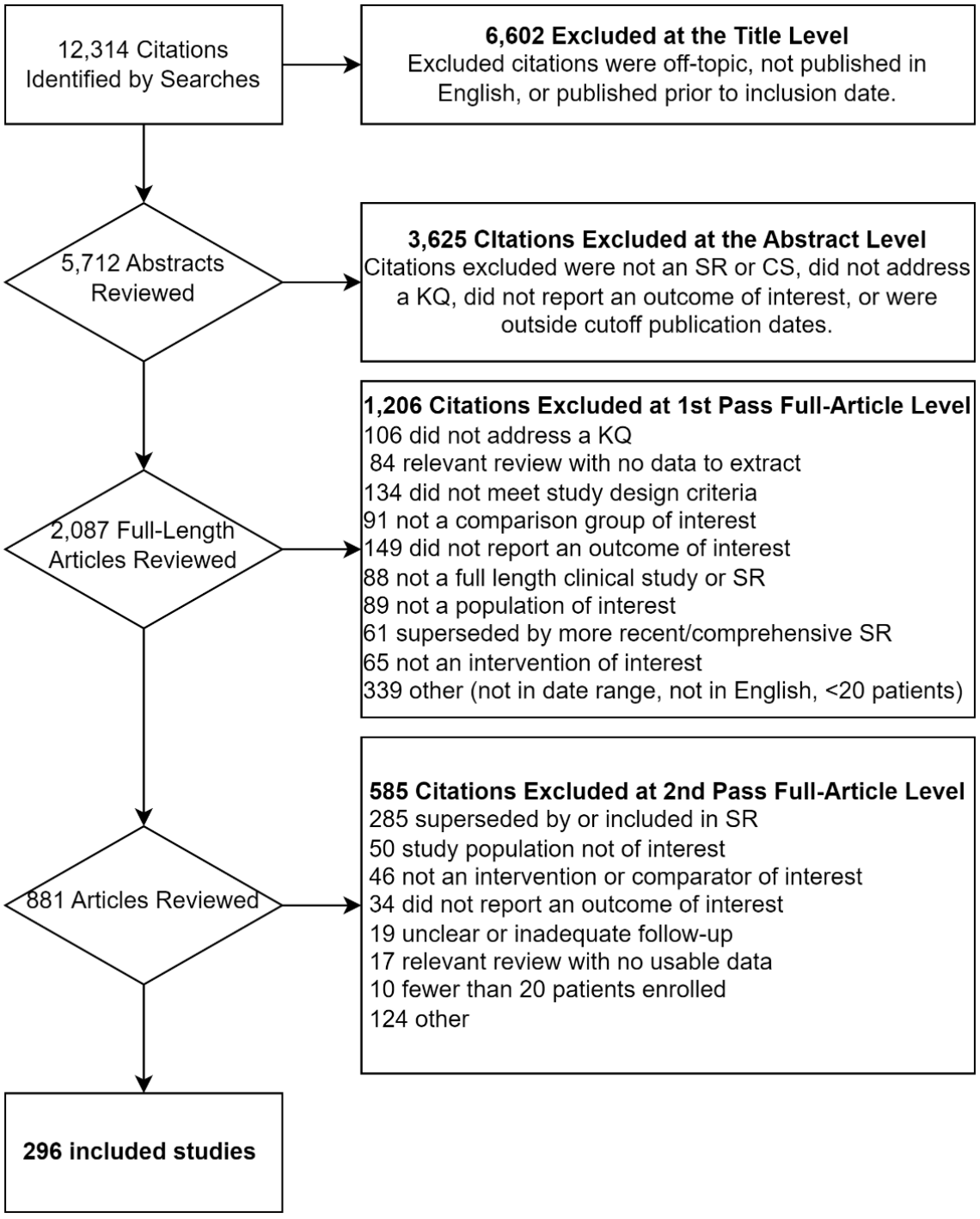
- Key Question 20
  - Critical outcomes
    - Symptom reduction or remission: positive, negative, and cognitive symptoms
  - Important outcomes
    - Functional status: vocational, educational, or both; social
    - Reduction in self-harm (including suicide)
    - QoL, wellbeing, and recovery
    - Treatment adherence
    - Relapse, recurrence, and hospitalization
    - Serious adverse events, including metabolic symptoms and cardiac events

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review. In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that

describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 12,314 citations identified by searches
    a. Right to Box 2: 6,602 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
    b. Down to Box 3
2. Box 3: 5,712 abstracts reviewed
    a. Right to Box 4: 3,625 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 2,087 full-length articles reviewed
    a. Right to Box 6: 1206 citations excluded at 1st pass full article level
        i. 106 did not address KQ
        ii. 84 relevant review with no data to abstract
        iii. 134 not study design of interest
        iv. 91 not a comparison group of interest
        v. 15 less than 20 patients
        vi. 149 did not report an outcome of interest
        vii. 88 not a full-length clinical study or SR
        viii. 89 not population of interest
        ix. 61 superseded by more recent/comprehensive review
        x. 65 not an intervention
        xi. 324 other (duplicates, not in date range, not in English)
    b. Down to box 7
4. Box 7: 881 articles reviewed
    a. Right to Box 8: 594 citations excluded at 2nd pass KQ level
        i. 50 not a study population of interest
        ii. 34 no outcomes of interest
        iii. 46 not an intervention or comparator of interest
        iv. 294 superseded by more comprehensive review or included in an SR

v. 17 relevant review with no usable data
vi. 19 unclear or inadequate follow-up
vii. 10 fewer than 20 patients
viii. 124 other (e.g., duplicate, published outside date range)

b. Down to box 9

5. Box 9: 296 Included studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For adults being assessed for prodromal symptoms or suspected psychosis, what is the diagnostic utility of different assessment tools, approaches, and biomarkers?	SRs: 3 RCTs: 0 Other: 7 cohort studies
2	Does use of treatment outcome measures improve outcomes for patients with schizophrenia? a) Which measures are most effective? b) What is the best frequency of measurements?	SRs: 1 RCTs: 1 Other: 3 (1 prospective controlled trial and 2 cohort studies)
3	What is the effectiveness of systems of care for managing first-episode psychosis?	SRs: 0 RCTs: 7
4	What is the effectiveness of team-based multi/interdisciplinary care for the management of individuals with schizophrenia?	SRs: 2 RCT: 4
5	For patients with schizophrenia, what is the effective medication, dose, and duration for first episode therapy and for a repeat episode of psychosis? For patients with schizophrenia, what is the effective dose and duration of maintenance therapy after a first episode and subsequent episodes?	SRs: 20 RCTs:11
6	For patients with schizophrenia, how do the effectiveness and comparative effectiveness and safety of antipsychotic medications (monotherapies and combined therapies) vary with patient characteristics for active treatment of acute episodes and for maintenance treatment to prevent relapses or recurrences?	SRs: 18 RCTs: 32
7	For patients with schizophrenia and schizoaffective disorder, which treatments are safe and effective for treating or preventing side effects from antipsychotic medication?	SRs: 7 RCTs: 4
8	For patients diagnosed with schizophrenia, what is the effectiveness and safety of non-pharmacologic therapies such as neuromodulatory or somatic interventions either alone or in combination with other therapies?	SRs: 2 RCTs: 3
9	For patients with schizophrenia and schizoaffective disorder, what strategies are effective for improving adherence?	SRs:1 RCTs: 4
10	What is the effectiveness and safety of psychotherapy for the treatment of schizophrenia?	SRs: 7 RCTs: 32

KQ Number	KQ	Number and Study Type
11	For patients with schizophrenia, what is the effectiveness and safety of a combination of psychotherapy and pharmacotherapy vs. psychotherapy or pharmacotherapy alone?	SRs: 0 RCTs: 6
12	What is the effectiveness and safety of treatment and support for families and caregivers of people with schizophrenia?	SRs: 3 RCTs: 4
13	What is the effectiveness and safety of peer provided interventions?	SRs: 0 RCTs: 2
14	What is the effectiveness and safety of community-based models of management?	SRs: 0 RCTs: 9
15	What is the effectiveness and safety of vocational rehabilitation?	SRs: 2 RCTs: 8
16	What is the effectiveness and safety of specific complementary and integrative health interventions for the treatment of schizophrenia?	SRs: 5 RCTs: 11
17	For patients with schizophrenia with cognitive impairments and/or negative symptoms, what are the effectiveness and comparative effectiveness and safety of treatments targeting these problems?	SRs: 12 RCTs: 29
18	For patients with schizophrenia, do interventions such as collaborative, team-based models, systematic monitoring, and patient engagement strategies improve outcomes related to health promotion, primary, secondary, and tertiary disease prevention, and treatment of co-occurring general health conditions?	SRs: 3 RCTs: 2
19	For patients with schizophrenia and comorbid SUD what are the effective programs for care delivery that improve health outcomes?	SRs: 1 RCTs: 0
20	What is the effectiveness and safety of technology-based interventions for patients with schizophrenia?	SRs: 7 RCTs: 14
	Total Evidence Base	**296 studies**

Abbreviations: RCT: randomized controlled trial; SR: systematic review; SUD: substance use disorder

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs published on or after November 1, 2011, to November 31, 2021. If multiple SRs addressed a key question, the most recent or comprehensive review or both were selected. SRs were supplemented with RCTs published subsequent to the SR.
- Studies had to be published in English.
- Only full clinical studies or SRs were included; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the Agency for Healthcare Research and

Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. An existing review was not used as evidence if it was impossible to assess the overall quality of the evidence in the review.

- For all key questions except KQ 1, a prospective, randomized controlled trial with an independent control group was required. Crossover trials were not included unless they reported data for the first phase of the study separately.
- In addition to RCTs and SRs, KQ 1 included observational diagnostic study designs that compared different assessment methods, tools, or both and their diagnostic accuracy for detection of schizophrenia in adults with prodromal symptoms or suspected psychosis.
- Study must have enrolled at least 20 patients (10 per study group for treatment studies, 20 total patients for diagnostic or prognostic studies); Small sample size is associated with increased risk of bias, and small studies were downgraded in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm.
- Newer Cochrane reviews already take into account small sample-size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, those data were not downgraded a second time.
- Study must have enrolled at least 85% of patients who met the study population criteria: adults with schizophrenia, schizophrenia spectrum disorders, schizoaffective disorder, schizophreniform symptoms, FEP, first-episode schizophrenia, or schizophrenia with catatonia, being treated in any setting. For studies examining mixed patient populations, studies must have enrolled at least 85% of patients with the relevant condition.
- Study must have reported at least one outcome of interest.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform, provider, or both can be found in Table A-3. See Appendix E for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform or Provider
Bibliographic Databases	EMBASE (Excerpta Medica) and MEDLINE	January 1, 2012, through December 31, 2021	Elsevier
	PsycINFO (for selected KQs)	January 1, 2012, through December 31, 2021	Ovid
	PubMed (in-process and Publisher records)	January 1, 2012, through December 31, 2021	NLM
Grey Literature	Agency for Healthcare Research and Quality (AHRQ)	January 1, 2012, through December 31, 2021	AHRQ
	U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	January 1, 2012, through December 31, 2021	VA

c. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the U.S. Preventive Services Task Force (USPSTF) method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(281)

Next, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, Defense Health Agency, the Lewin Team convened *a* four-day virtual recommendation development meeting from June 6–9, 2022, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains.(50) Information on each domain, questions to consider, and the resulting judgement can be found in Table A-4.

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include *High*, *Moderate*, *Low*, or *Very Low*. These four ratings are a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(52, 53)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very Low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(50)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include *benefits outweigh harms/burdens*, *benefits slightly outweigh harms/burdens*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most providers will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they might apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include *similar values*, *some variation*, and *large variation*. For instance, there might be *some variation* in patient values and preferences for a recommendation on the use of acupuncture because some patients might dislike needles. When patient values seem homogeneous, this domain might increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain might decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix B).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain, for example, include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population might be geographically remote from an intervention (e.g., complex radiological equipment); a drug might be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	• Among the designated critical outcomes, what is the lowest quality of relevant evidence? • How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very Low
Balance of desirable and undesirable outcomes	• What is the magnitude of the anticipated desirable outcomes? • What is the magnitude of the anticipated undesirable outcomes? • Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	• Benefits outweigh harms/burdens • Benefits slightly outweigh harms/burdens • Benefits and harms/burdens are balanced • Harms/burdens slightly outweigh benefits • Harms/burdens outweigh benefits
Patient values and preferences	• What are the patients' values and preferences? • Are values and preferences similar across the target population? • Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• What are the costs per resource unit? • Is this intervention generally available? • What is the variability in resource requirements across the target population and settings? • Are the resources worth the expected net benefit from the recommendation? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 3. For this new CPG, all recommendations were categorized as *Reviewed, New-added*

(see Recommendations). *Reviewed*, *New-added* recommendations are original, new recommendations based entirely on evidence included in the systematic evidence review.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG, as appropriate, to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, quick reference guide, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in April 2023.

Appendix B: 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 B-1) 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 B-1. 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

Appendix C: 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.

Appendix D: Pharmacotherapy

Table D-1: 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 D-2: 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, 1064 mg I (Aristada Initio): 675 mg single dose	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.
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.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
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	
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.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
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 D-3: 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	+	++	+

[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.

Medication	EPS	Sedation	Weight Gain	Metabolic	Orthostasis	AcH	QTc
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

Table D-4: 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
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 D-5: 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 D-6: 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.
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

[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 (cont.)	***Aripiprazole lauroxil***	Gluteal 441 mg dose may be given in the deltoid	• 10 mg/day = 441 mg/month • 15 mg/day = 662 mg/month, 882 mg/6 weeks, OR 1,064 mg/2 months • >/= 20 mg/day = 882 mg/ month • 675mg IM given in combination with a single 30mg PO dose	• 441–882 mg/month • 882 mg every 6 weeks • 1,064 mg every 2 months	882 mg/month	In conjunction with the first LAI dose, take 30mg PO and 675mg IM OR 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
	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

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics (cont.)	***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
	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

Medication		Injection Site	Initial Dose	Maintenance Dose	Maximum Dose	Oral Overlap
Second-Generation Antipsychotics (cont.)	***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.
	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

Appendix E: Consensus on Balancing Ethical Principles of Respect for Autonomy and Beneficence

In working to develop recommendations for the care that should be provided to individuals with schizophrenia, the Work Group came to consensus that the principles underlying the approaches to care specified in this CPG should be supplemented by a statement on the need to balance the ethical principles of respect to autonomy and beneficence while providing care for individuals with schizophrenia and others with serious mental illnesses.

The emphases on patient-centered care and shared decision making in the Approach to Care in Department of Veterans Affairs and Department of Defense section reflect VA and DoD commitment to provide mental health care based on the ethical principle of respect for autonomy that helps individuals with mental health conditions lead the kind of lives they prefer, despite diagnoses, symptoms, and impairments. However, it is important to recognize that schizophrenia can be complicated by episodes associated with impairments in judgment, decision making capacity, and impulse control that can lead to suicide, self-harm, self-neglect, or danger to others. When these episodes occur, too great an emphasis on respect for autonomy can place lives at risk, and providers are obliged to prioritize actions to prevent harm, including involuntary hospitalization, when needed, based on the principle of beneficence, that is, on doing what is right for the individual with a mental health condition, even when they disagree.

Although health care providers in VA and DoD practice within federal facilities, state law defines the indications and procedures for involuntary hospitalization and treatment for mental health conditions in VA and community-based acute mental health inpatient services. These indications and procedures differ from state to state, and they are evolving. The policies for federal military treatment facilities are distinct. At the time of writing of this CPG, involuntary hospitalization in these facilities requires that an active duty Service member has, or likely has, a severe mental disorder or poses imminent or potential danger to self or others, and placement in a less restrictive level of care would result in inadequate medical care. Procedures are detailed in DoD instructions and must be consistent with applicable CPGs.(282) Providers must be aware of these laws and policies and must be prepared to act on them when necessary.

Even when it is necessary, prioritization of beneficence over autonomy to prevent harm must be limited to times when risks and relevant symptoms or impairments continue to be present and to specific elements of care covered by state law or, for military treatment facilities, federal policy. Outside these limits, care should remain patient centered and based on principles of recovery and respect for autonomy.

Treatment planning for individuals with schizophrenia should include a focus on enhancing autonomy and preventing dangerous degrees of deterioration through ongoing attention to the treatment alliance and engagement in maintenance treatment.

Additionally, providers should consider the use of behavioral health advance directives (283) that allow individuals with mental health conditions to proactively document their preferences for future treatment in the event of impairments that limit autonomy or Wellness Recovery Action Plans that provide proactive help with self-management for individuals with mental health conditions and that assist providers with promoting autonomy.(284)

Appendix F: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited one participant for the focus group, with support from the Champions and other Work Group members, as needed. Although participant recruitment focused on eliciting a range of perspectives likely relevant and informative in the CPG development process, the patient focus group participant was not intended to be a representative sample of VA and DoD patients. The participant was not incentivized for participation or reimbursed for travel expenses. The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed, and the Work Group approved a patient focus group guide covering these topics. The focus group facilitator led the discussion used the guide to elicit patient perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. The participant explained that goals should encompass foundational elements of being able to live, work, and learn. Individuals with schizophrenia need to maintain life skills and to be consistent.

- The participant emphasized the importance of prioritizing consistency in treatment before pursuing other goals because achieving consistency in treatment is a necessary foundational step.
- The participant indicated that a goal of developing and maintaining life skills is important for overcoming the daily struggles associated with schizophrenia so other goals can be pursued.

b. The participant believed that peer support, recovery models, and interdisciplinary models of care (e.g., Mental Health Intensive Case Management [MHICM], Psychosocial Rehabilitation and Recovery Center [PRRC], the Bridger Program) are effective and should be used together.

- The participant emphasized the benefits of peer support for people with schizophrenia.
- The participant recommended modeling treatment programs after Mental Health Intensive Case Management (MHICM), Psychosocial Rehabilitation and Recovery Center (PRRC), and the Bridger Program because these models of care seem to be effective.

c. The participant described the benefit of treatment plans that emphasize non-pharmacotherapy–based coping strategies (e.g., meditation, yoga, art therapy) in combination with pharmacotherapy.

- The participant noted that incorporating a variety of non-pharmacotherapy–based practices is beneficial for the treatment of schizophrenia.

- The participant believed that consistent use of medication is essential.

d. The participant stated that using shared decision making and a psychoeducational approach involving providers, patients, and their families for managing a person's schizophrenia is important for achieving goals and functional recovery.

- The participant noted that family involvement throughout the duration of treatment and strong relationships between patients and providers are critical for functional recovery.
- The participant indicated that combining traditional education modalities with more collaborative learning environments—allowing providers, patients, and families to learn from each other—is important for patients to understand their schizophrenia diagnosis.

e. The participant noted a preference for a hybrid model of virtual and in-person care that allows flexibility for patients in their treatment modality.

- The participant appreciated having the option to interact with their provider virtually or in-person.

f. The participant noted that increased care coordination, record sharing, and interdisciplinary support from providers would improve care delivery for patients.

- The participant expressed frustration with the limitations imposed on record sharing and care coordination among different health care organizations.
- The participant highlighted the importance of supporting providers to enhance the quality of care patients receive.

g. The participant noted a critical need for better follow-up and continuity of care across the health care system, including transition from DoD to VA.

- The patient emphasized the need for better follow-up care for patients receiving treatment for schizophrenia.
- The participant expressed frustration with continuity of care across the health care system.

Appendix G: Evidence Table

Table G-1: Evidence Table[a,b,c]

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
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.	(67-73)	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.	(73-75)	Neither for nor against	Reviewed, New-added
3.	We recommend treatment/management with early intervention services for individuals with first-episode psychosis.	(76, 77) **Additional references** (78, 79)	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.	(80-82)	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.	(84-87) **Additional references** (83, 88)	Weak for	Reviewed, New-added

[a] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference had to be identified through a systematic evidence review carried out as part of the development of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation but that were not identified through the systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[b] Strength of Recommendation column: The VA/DoD Schizophrenia CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Determining Recommendation Strength and Direction section for more information.

[c] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process, the categories, and their definitions.

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
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.	(89, 90)	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.	(91)	Neither for nor against	Reviewed, New-added
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.	(91-107) **Additional reference** (108)	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.	(95–98, 107, 109–114) **Additional reference** (108)	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.	(76, 91-93, 95-106, 115-118) **Additional references** (119, 120)	Weak for	Reviewed, New-added
11.	We suggest offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia.	(121) **Additional reference** (122)	Weak for	Reviewed, New-added
12.	We recommend the use of clozapine for individuals with treatment-resistant schizophrenia.	(126, 127) **Additional references** (123-125, 128-140)	Strong for	Reviewed, New-added

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
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.	(141-144)	Weak for	Reviewed, New-added
14.	There is insufficient evidence to recommend for or against any treatment for hyperprolactinemia-related side effects.	(145, 146) **Additional reference** (147)	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.	(148, 149)	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.	(150-154)	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.	(155)	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.	(156-163)	Neither for nor against	Reviewed, New-added
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.	(164)	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.	(165, 166) **Additional references** (167-170)	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.	(175, 176) **Additional references** (83, 88, 177-181)	Strong for	Reviewed, New-added

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
22.	There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with schizophrenia experiencing housing insecurity.	(183, 184) **Additional references** (182, 185-187)	Neither for nor against	Reviewed, New-added
23.	We suggest compensatory cognitive training programs for the treatment of cognitive impairment for individuals with schizophrenia.	(190-194) **Additional references** (188, 189)	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.	(193-202, 204) **Additional reference** (205)	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.	(206-211)	Neither for nor against	Reviewed, New-added
26.	There is insufficient evidence to recommend for or against electroconvulsive therapy for individuals with schizophrenia.	(212) **Additional reference** (214)	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.	(84, 164, 215-219)	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.	**(**174**,** 223**,** 224**)** **Additional references** (220, 221)	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.	(174, 223, 224) **Additional references** (171-173, 225-227)	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.	(230, 232-234, 285)	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.	(235-237)	Weak for	Reviewed, New-added

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
32.	We suggest cognitive behavioral therapy for psychosis in combination with pharmacotherapy for individuals with prodromal and early psychosis.	(235-237)	Weak for	Reviewed, New-added
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.	(141, 195, 235, 236, 238, 239, 242-244, 248-255, 257, 258) **Additional references** (240, 241, 245-247, 256)	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.	(259-263)	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.	(264-266)	Neither for nor against	Reviewed, New-added
36.	We suggest using telephone-based care management to reduce rehospitalization days for individuals with schizophrenia.	(267-269)	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.	(270)	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.	(219, 272, 273) **Additional reference** (271)	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.	(275, 276) **Additional reference** (274)	Strong for	Reviewed, New-added

#	Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
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.	(148, 276) **Additional reference** (277)	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.	(278)	Neither for nor against	Reviewed, New-added

Appendix H: Participant List

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Appendix I: Literature Review Search Terms and Strategy

Table I-1. EMBASE and MEDLINE in EMBASE.com Syntax

KQ	Set	Concept	Strategy
KQ 1	#1	Prodromal Symptom/ Early Onset/First-Episode Psychosis	'prodromal symptom'/de AND ('schizophrenia'/de OR 'schizoaffective psychosis'/de) OR ((early OR emergent OR emerging OR first OR prodrom*) NEAR/5 (psychos* OR psychotic* OR schiz*))
	#2	Assessment Tools/Approaches	bsabs OR 'bonn scale for the assessment of basic symptoms' OR das OR 'disability assessment schedule' OR 'early psychosis screen*' OR 'interview for the retrospective assessment of the onset and course of schizophrenia and other psychoses' OR iraos OR 'mass screening'/exp OR 'mini panss' OR panss OR pirs OR 'positive and negative symptom scale' OR 'positive and negative syndrome scale' OR 'present state examination' OR 'prime screen*' OR (pq* AND questionnaire*) OR pse OR prodscreen OR 'prodromal questionnaire' OR 'psychological impairments rating schedule' OR 'psychological rating scale'/de OR sads OR 'scale for the assessment of negative symptoms' OR 'schedule for affective disorders and schizophrenia' OR 'scid i p' OR 'scid p' OR 'screening test'/exp OR sips OR 'structured interview for prodromal symptoms' OR ('structured clinical interview' AND 'patient edition') OR 'structured interview for psychosis risk' OR 'questionnaire'/de OR ((assess* OR confirm* OR detect* OR diag* OR rating OR suspect* OR screen*) NEAR/3 (scale OR scales OR index OR indices OR instrument* OR questionnaire* OR survey* OR tool*))
	#3	Biomarkers	'biological marker'/de OR biomarker* OR cortisol OR electroenceph* OR 'electroencephalogram'/de OR eeg OR endocrine OR fmri OR 'functional magnetic resonance imaging'/de OR 'genome-wide association study'/de OR gwas OR 'hydrocortisone'/de OR 'magnetic resonance imag*' OR melatonin OR mri OR 'nuclear magnetic resonance imaging'/de OR pet OR 'positron emission tomography'/de OR thyroid*
	#4	Diagnosis	'accuracy':de OR (area NEXT/1 under NEXT/3 curve) OR auc OR 'diagnosis'/exp/mj OR diagnos*:ti OR 'diagnostic accuracy' OR 'diagnostic error*' OR 'diagnostic error'/exp OR 'diagnostic test accuracy':de OR 'differential diagnosis'/exp OR ((false OR true) NEAR/1 (positive OR negative)) OR likelihood OR 'maximum likelihood method':de OR ppv OR precision OR 'precision'/exp OR 'prediction and forecasting' OR 'prediction and forecasting'/exp OR 'predictive value'/exp OR 'predictive value' OR 'receiver operating characteristic' OR 'receiver operating characteristic':de OR 'roc curve' OR 'roc curve'/exp OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity')
	#5	Combine Concepts	#1 AND (#2 OR #3 OR #4)
	#6	Remove Animal Studies	#5 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))

KQ	Set	Concept	Strategy
KQ 1 (cont.)	#7	Remove Pediatric Population	#6 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#8	Remove Unwanted Publication Types	#7 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#9	Cohort Studies and Diagnostic Accuracy Studies and Meta Analyses and Systematic Reviews	#8 AND ('cohort analysis'/exp OR 'diagnostic accuracy'/exp OR 'meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR cohort*:ab,ti OR 'diagnostic accuracy':ab,ti OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#10	Limit to Randomized Controlled Trials	#8 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#11	Combine Concepts	#9 OR #10
	#12	Apply Date Limits	#11 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#13	Limit to English	#11 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 2	#14	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 2 (cont.)	#15	Measures	'arizona sexual experience scale' OR asex OR assess*:ti OR assessment*:ti OR bam OR 'basis-24' OR 'basis-32' OR 'behavior and symptom identification scale' OR 'biological marker'/exp OR biomarker*:ti OR (blood NEAR/3 (sample* OR test*)) OR 'blood pressure'/exp OR 'blood pressure' OR 'blood sampling'/exp OR 'blood urea nitrogen' OR bmi OR 'body mass'/de OR 'body mass index' OR bprs OR 'brief addiction monitor' OR 'brief psychiatric rating scale' OR bun OR 'epworth sleepiness scale'/exp OR 'epworth sleepiness scale' OR ess OR 'fasting glucose' OR gaf OR (gap NEAR/3 measur*) OR 'global assessment of functioning' OR 'glucose blood level'/de OR (glucose NEAR/3 (level* OR test*)) OR hga1c OR 'indiana job satisfaction scale' OR instrument*:ti OR index:ti OR 'kidney function test'/exp OR 'leukocyte count'/exp OR 'leukopenia'/exp OR 'lipid blood level'/exp OR (lipid* NEAR/3 (level* OR test*)) OR 'liverpool university neuroleptic side-effect rating scale' OR luners OR lunsers OR mcsi OR measure*:ti OR 'measurement based care' OR 'medication possession ratio' OR mems OR 'mental illness research, education, and clinical center' OR (microelectronic NEAR/3 monitor* NEAR/3 system*) OR mirecc OR 'modified colorado symptom index' OR monitor*:ti OR (monitor* NEAR/2 (outcome* OR progress)) OR mpr OR 'named inventories, questionnaires and rating scales'/exp OR 'outcome assessment'/exp OR (outcome* NEAR/3 (assess* OR measure* OR patient* OR test*)) OR panns OR 'parameters'/de OR 'patient health questionnaire'/exp OR 'patient health questionnaire' OR 'patient monitoring'/de OR 'phq':ti,ab OR 'positive and negative syndrome scale' OR 'progress feedback' OR 'psychological rating scale'/exp/mj OR (('quality of life' OR qol) NEAR/5 (interview* OR scale*)) OR 'questionnaire'/exp OR questionnaire*:ti OR 'rating scale'/de OR 'recovering quality of life' OR 'reqol-10' OR sas OR 'satisfaction with life scale'/de OR scale:ti OR scales:ti OR (scale* NEAR/3 (disab* OR function* OR symptom*)) OR 'self monitoring'/exp OR 'self report'/exp/mj OR 'social attainment scale' OR 'urea nitrogen blood level'/de OR 'urinalysis'/exp OR (urine NEAR/3 (sample* OR test*)) OR wbc OR 'white blood cell count' OR whodas OR 'world health organization disability assessment schedule'
	#16	Combine Concepts	#14 AND #15
	#17	Remove Animal Studies	#16 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#18	Remove Pediatric Population	#17 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Strategy
KQ 2 (cont.)	#19	Remove Unwanted Publication Types	#18 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#20	Limit to Randomized Controlled Trials	#19 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#21	Limit to Meta Analyses and Systematic Reviews	#20 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#22	Combine Concepts	#20 OR #21
	#23	Apply Date Limits	#22 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#24	Limit to English Language	#22 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 3	#25	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#26	Team-Based Multidisciplinary/ Interdisciplinary Care	((care OR team* OR treatment*) NEAR/2 (collaborat* OR coordinat* OR integrat* OR interdisciplin* OR model* OR multidisciplin*)) OR 'case management'/de OR coach*:ti OR 'collaborative care team'/exp OR 'coordinated specialty care' OR (csc AND coordinated) OR (('enhancing quality' OR equip) NEAR/4 psychosis) OR 'health coach*' OR 'individualized case management' OR 'interdisciplinary care'/exp OR 'medical home*' OR 'multidisciplinary team'/exp OR pact OR 'patient aligned care team' OR 'patient centered medical home' OR (pcmh AND 'medical home') OR team*:ti OR 'team based' OR (team* NEAR/2 care) OR 'whole health'

KQ	Set	Concept	Strategy
KQ 3 (cont.)	#27	Combine Concepts	#25 AND #26
	#28	Remove Animal Studies	#27 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#29	Remove Pediatric Population	#28 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#30	Remove Unwanted Publication Types Remove Unwanted Publication Types	#29 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#31	Limit to Randomized Controlled Trials	#30 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#32	Limit to Meta Analyses and Systematic Reviews	#31 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#33		#31 OR #32
	#34	Apply Date Limits	#33 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#35	Limit to English	#33 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 4	#36	Prodromal Symptom/Early Onset/First-Episode Psychosis	'prodromal symptom'/de AND ('schizophrenia'/de OR 'schizoaffective psychosis'/de) OR ((emergent OR emerging OR prodrom* OR early OR first) NEAR/5 (psychos* OR psychotic* OR schiz*))
	#37	Systems of Care	(care NEAR/3 (coordinated OR system*)) OR 'connection program' OR 'coordinated care'/de OR 'coordinated specialty care' OR (csc AND coordinated) OR 'early assessment and support alliance' OR easa OR navigate OR ontrackny OR 'on track ny' OR 'recovery after initial schizophrenia episode' OR ra1se OR 'raise connection' OR 'specialized treatment early in psychosis'

KQ	Set	Concept	Strategy
KQ 4 (cont.)	#38	Combine Concepts	#36 AND #37
	#39	Remove Animal Studies	#38 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#40	Remove Pediatric Population	#39 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#41	Remove Unwanted Publication Types	#40 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#42	Limit to Randomized Controlled Trials	#41 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#43	Limit to Meta Analyses and Systematic Reviews	#41 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#44		#42 OR #43
	#45	Apply Date Limits	#44 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#46	Limit to English	#44 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim

KQ	Set	Concept	Strategy
KQ 5, 6, and 7	#47	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni* OR psychoses OR psychosis OR psychotic* OR schizoaffective OR schizofren* OR schizoid* OR schizophasia* OR schizophrenia* OR schizophrenic* OR schizophreniform OR schizotyp* OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#48	Antipsychotics (General)	'neuroleptic agent'/exp OR 'anti psychotic*' OR antipsychotic* OR neuroleptic*
	#49	First-Generation Antipsychotics	chlorpromazine OR fluphenazine OR 'fluphenazine decanoate' OR 'fluphenazine lai' OR haldol OR haloperidol OR 'haloperidol decanoate' OR 'haloperidol lai' OR loxapine OR mellaril OR molindone OR navane OR perphenazine OR pimozide OR prolixin OR thioridazine OR thiothixene OR tiotixene OR stelazine OR thorazine OR trifluoperazine OR trilafon OR ((conventional OR '1st generation' OR 'first generation' OR typical) NEAR/2 ('anti psychotic*' OR antipsychotic* OR neuroleptic*))
	#50	Second-Generation Antipsychotics	abilify OR abilitat OR amisulpride OR aripiprazole OR 'aripiprazole lauroxil' OR 'aripiprazole monohydrate' OR aristada OR asenapine OR barhemsys OR blonanserin OR brexpiprazole OR caplyta OR cariprazine OR ciatyl OR cisordinol OR clopixol OR clozapine OR clozaril OR emilace OR fanapt OR fazaclo OR geodon OR iloperidone OR 'invega sustenna' OR 'invega trinza' OR lapenax OR leponex OR latuda OR lonasen OR lullan OR lumateperone OR 'lumateperone tosylate' OR lurasidone OR midax OR nemonapride OR nipolept OR olansek OR olanzapine OR 'olanzapine lai' OR 'olanzapine pamoate' OR paliperidone OR 'paliperidone lai' OR 'paliperidone palmitate' OR peridone OR perospirone OR pimavanserin OR quetiapine OR rexulti OR risperdal OR risperidone OR 'risperidone lai' OR rispolept OR saphris OR secuado OR serdolect OR serlect OR seroquel OR sertindole OR sycrest OR trevicta OR versacloz OR vraylar OR xeroquel OR zalasta OR zeldox OR ziprasidone OR zoleptil OR zomaril OR zotepine OR zuclopenthixol OR zydis OR zypadhera OR zyprex OR zyprexa OR ((atypical OR '2nd generation' OR 'second generation') NEAR/2 ('anti-psychotic*' OR antipsychotic* OR neuroleptic*))
	#51	Combine Concepts	#47 AND (#48 OR #49 OR #50)
	#52	Remove Animal Studies	#51 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#53	Limit to English	#52 AND [english]/lim

KQ	Set	Concept	Strategy
KQ 5, 6, and 7 (cont.)	#54	Remove Pediatric Population	#53 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#55	Remove Unwanted Publication Types	#54 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#56	Limit to Randomized Controlled Trials	'random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab
	#57	Limit to Meta Analyses and Systematic Reviews	('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#58	Combine Concepts	#55 AND (#56 OR #57)
	#59	Apply Date Limits	#58 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
KQ 8	#60	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 8 (cont.)	#61	Neuromodulatory/ Somatic Interventions	'brain depth stimulation'/de OR 'electric shock'/de OR 'electroconvulsive therapy'/de OR 'neuromodulation'/de OR 'repetitive transcranial magnetic stimulation'/de OR 'transcranial direct current stimulation'/de OR 'transcranial magnetic stimulation'/de OR 'vagus nerve stimulation'/de OR (('brain depth' OR 'deep brain' OR electroconvulsive OR transcranial OR 'vagus nerve') NEAR/3 (stimulat* OR therap* OR treatment*)) OR neuromodulat* OR dbs:ti OR ect:ti OR rtms:ti OR tdcs:ti OR tms:ti OR vns:ti OR ((dbs OR ect OR rtms OR tdcs OR tms OR vns) AND stimulat*)
	#62	Combine Concepts	#60 AND #61
	#63	Remove Animal Studies	#62 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#64	Limit to English	#63 AND [english]/lim
	#65	Remove Pediatric Population	#64 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#66	Remove Unwanted Publication Types	#65 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#67	Limit to Randomized Controlled Trials	'random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab
	#68	Limit to Meta Analyses and Systematic Reviews	('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#69	Combine Concepts	#66 AND (#67 OR #68)
	#70	Apply Date Limits	#69 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd

KQ	Set	Concept	Strategy
KQ 9	#71	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#72	Adherence	'medication adherence monitoring system'/de OR 'medication compliance'/exp OR 'mental compliance'/de OR 'motivational interviewing'/de OR 'patient attitude'/de OR 'patient compliance'/de OR 'patient preference/de' OR 'reminder system'/de OR 'shared decision making'/de OR 'treatment refusal'/de OR 'wearable sensor'/de OR ((appointment* OR medication* OR treatment* OR therap*) NEAR/2 (adher* OR agree* OR attend* OR complian* OR complied OR complies OR comply OR cooperat* OR disagree* OR 'non adher*' OR nonadher* OR noncomplian* OR prefer* OR refus* OR reject* OR remind* OR uncooperat*)) OR (patient* NEAR/2 (adher* OR agree* OR attend* OR complian* OR complied OR complies OR comply OR cooperat* OR disagree* OR 'non adher*' OR nonadher* OR 'non complian*' OR noncomplian* OR prefer* OR refus* OR reject* OR remind* OR uncooperat*)) OR adher*:ti OR attend*:ti OR complian*:ti OR complied:ti OR complies:ti OR comply:ti OR 'non adher*':ti OR nonadher*:ti OR noncompl*:ti OR refus*:ti OR remind*:ti OR 'pill box*' OR pillbox* OR (remind* NEAR/2 (appointment* OR patient* OR medication* OR medicine* OR pill*)) OR (supervis* NEAR/2 (medication* OR medicine* OR pill*)) OR (court NEAR/2 (order* OR mandat*) NEAR/2 (medication* OR medicine* OR pill* OR therap* OR treatment*)) OR 'blister pack*':ab,ti OR ((electronic* NEXT/1 monitor*):ab,ti)
	#73	Long-Acting Injectibles	'long acting drug'/de OR ((depot OR intramuscular* OR 'long acting') NEAR/2 (administ* OR 'anti-psychotic*' OR antipsychotic* OR dosage* OR dose* OR dosing* OR drug* OR inject* OR medicine* OR pharm* OR medication* OR neuroleptic*))
	#74	Combine Concepts	#71 AND (#72 OR #73)
	#75	Remove Animal Studies	#74 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))

KQ	Set	Concept	Strategy
KQ 9 (cont.)	#76	Remove Pediatric Population	#75 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#77	Remove Unwanted Publication Types	#76 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#78	Limit to Randomized Controlled Trials	#77 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#79	Limit to Meta Analyses and Systematic Reviews	#77 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#80	Combine Concepts	#78 OR #79
	#81	Limit to English	(#78 OR #79) AND [english]/lim
	#82	Apply Date Limits	#81 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
KQ 10	#83	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 10 (cont.)	#84	Psychotherapy	'acceptance and commitment therapy'/de OR 'art therapy'/de OR 'cognitive behavioral therapy'/exp OR 'cognitive remediation therapy'/de OR 'psychotherapy'/exp OR 'social competence'/de OR 'social cognition'/de OR (((art OR cognitiv* OR metacognitive* OR psychosocial* OR positiv* OR resilien* OR social*) NEAR/2 (counsel* OR therap* OR psychol* OR psychother* OR teach* OR train* OR treat* OR rehab*)):ti) OR (cbtp:ti AND cognitive:ti) OR ((cognitive NEAR/2 (behav* OR rehab* OR remediat*)):ti) OR ((skill* NEAR/2 train*):ti) OR psychotherap*:ti OR 'acceptance and commitment' OR 'illness management and recovery' OR wellfocus
	#85	Combine Concepts	#83 AND #84
	#86	Remove Animal Studies	#85 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#87	Limit to English	#86 AND [english]/lim
	#88	Remove Pediatric Population	#87 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#89	Remove Unwanted Publication Types	#88 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#90	Limit to Randomized Controlled Trials	'random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab
	#91	Limit to Meta Analyses and Systematic Reviews	('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#92	Combine Concepts	#89 AND (#90 OR #91)
	#93	Apply Date Limits	#92 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd

KQ	Set	Concept	Strategy
KQ 11	#94	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni* OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#95	Combination Therapy/ Monotherapy	'add on therapy'/de OR 'drug combination'/de OR monotherap* OR 'monotherapy'/de OR polypharm* OR 'polypharmacy'/de OR (((add OR 'add on' OR added OR adding OR additional OR adds OR adjunct* OR augment* OR blend* OR combin* OR incorporat* OR integrat* OR mix*) NEAR/1 ('anti psychotic*' OR antipsychotic* OR behav* OR cognitive OR counsel* OR drug* OR medicine* OR medication* OR 'mental health' OR neuroleptic* OR pharm* OR psychiatric* OR psychol* OR psychother* OR therap* OR treatment*)):ab,ti) OR 'add on':ti OR adjunct*:ti OR augment*:ti OR combin*:ti OR polypharm*:ti OR supplement*:ti OR ('psychotherapy'/de AND 'neuroleptic agent'/de)
	#96	Combine Concepts	#94 AND #95
	#97	Remove Animal Studies	#96 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#98	Remove Pediatric Population	#97 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#99	Remove Unwanted Publication Types	#98 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))

KQ	Set	Concept	Strategy
KQ 11 (cont.)	#100	Limit to Randomized Controlled Trials	#99 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#101	Limit to Meta Analyses and Systematic Reviews	#99 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#102	Combine Concepts	#100 OR #101
	#103	Limit to English	#102 AND [english]/lim
	#104	Apply Date Limits	#103 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
KQ 12	#105	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#106	Families and Caregivers	'couple therapy'/de OR 'family therapy'/de OR 'integrative behavioral couple* therapy' OR 'integrative behavioural couple* therapy' OR ibct OR 'veteran-centered brief family consultation' OR (('multi family' OR multifamily) NEXT/2 therapy) OR (('caregiver'/exp OR caregiver*:ti) AND ('group therapy'/de OR intervention* OR 'psycho edu*' OR psychoedu* OR program*:ti OR support* OR therapy)) OR (('family'/de OR family:ti OR families:ti) AND (intervention* OR 'psycho ed*' OR psychoed* OR therapy))
	#107	Combine Concepts	#105 AND #106
	#108	Remove Animal Studies	#107 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))

KQ	Set	Concept	Strategy
KQ 12 (cont.)	#109	Remove Pediatric Population	#108 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#110	Remove Unwanted Publication Types	#109 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#111	Limit to Randomized Controlled Trials	#110 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#112	Limit to Meta Analyses and Systematic Reviews	#110 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#113	Combine Concepts	#111 OR #112
	#114	Apply Date Limits	#113 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#115	Limit to English	#113 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 13	#116	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 13 (cont.)	#117	Peer-Provided Interventions	'12 step*' OR 'twelve step' OR 'peer support' OR 'mutual support' OR (peer* NEAR/4 (intervention* OR led OR program* OR provider* OR respite* OR run OR specialist* OR support*)) OR 'recovery international' OR 'self help'/exp OR 'self help' OR 'vet to vet'
	#118	Combine Concepts	#116 AND #117
	#119	Remove Animal Studies	#118 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#120	Remove Pediatric Population	#119 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#121	Remove Unwanted Publication Types	#120 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#122	Limit to Randomized Controlled Trials	#121 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#123	Limit to Meta Analyses and Systematic Reviews	#121 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#124	Combine Concepts	#122 OR #123
	#125	Apply Date Limits	#124 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#126	Limit to English	#124 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim

KQ	Set	Concept	Strategy
KQ 14	#127	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/de OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/de OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#128	Community-Based Models of Management	act:ab,kw,ti AND 'assertive community':ab,kw,ti OR 'assertive community treatment'/exp OR 'assertive community treatment':ab,kw,ti OR ((care OR case) NEAR/3 manage*) OR ('case manage*' NEAR/3 (community OR home)) OR 'community based services' OR 'community care'/de OR 'enhanced rural access network for growth enhancement':ab,kw,ti OR 'housing first':ab,kw,ti OR ((housing NEAR/3 (congregate OR group OR supported)):ab,kw,ti) OR 'integrated community case management' OR 'intensive case management'/exp OR 'intensive case management':ab,kw,ti OR 'mental health intensive case management':ab,kw,ti OR mhicm:ab,kw,ti OR pact OR ((strength* NEAR/3 case NEAR/3 management):ab,kw,ti)
	#129	Combine Concepts	#127 AND #128
	#130	Remove Animal Studies	#129 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#131	Remove Pediatric Population	#130 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#132	Remove Unwanted Publication Types	#131 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))

KQ	Set	Concept	Strategy
KQ 14 (cont.)	#133	Limit to Randomized Controlled Trials	#132 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#134	Limit to Meta Analyses and Systematic Reviews	#132 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#135	Combine Concepts	#133 OR #134
	#136	Apply Date Limits	#135 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#137	Limit to English	#135 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 15	#138	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#139	Vocational Rehabilitation	clubhouse OR 'employment'/exp OR employment:ti,ab OR employ:ti,ab OR employed:ti,ab OR job:ti,ab OR 'individual placement and support'/exp OR 'individual placement and support' OR 'pre-vocational training' OR 'supported employment'/exp OR (transition* NEAR/3 (employ* OR work* OR job)) OR 'work status' OR vocation* OR 'vocational rehabilitation'/exp OR 'voluntary worker'/exp OR 'volunteer'/exp OR volunteer* OR 'work'/exp OR workplace
	#140	Combine Concepts	#138 AND #139
	#141	Remove Animal Studies	#140 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))

KQ	Set	Concept	Strategy
KQ 15 (cont.)	#142	Remove Pediatric Population	#141 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#143	Remove Unwanted Publication Types	#142 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#144	Limit to Randomized Controlled Trials	#143 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#145	Limit to Meta Analyses and Systematic Reviews	#143 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#146	Combine Concepts	#144 OR #145
	#147	Apply Date Limits	#146 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#148	Limit to English	#146 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 16	#149	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 16 (cont.)	#150	Complementary and Integrative Health Interventions	('acupuncture'/exp OR acupuncture OR 'alternative medicine'/mj/exp OR 'integrative medicine'/de OR ((alternative OR complementary OR integrative) NEAR/2 (care OR health OR intervention* OR medic* OR model* OR regimen* OR treatment* OR therap*)) OR 'exercise'/exp) AND 'meditation'/de OR meditate* OR 'mindfulness'/exp OR 'mindfulness based stress reduction'/de OR 'problem solving'/exp OR 'problem solving' OR relax* OR relaxation OR 'relaxation training'/de OR 'sleep hygiene'/exp OR 'tai chi' OR 'tai chi'/de OR yoga OR 'yoga'/de OR (stress* NEAR/3 (alleviat* OR decreas* OR manage* OR reduc*))
	#151	Complementary and Integrative Health Interventions (General)	'alternative medicine'/exp OR 'cim' OR 'cam' OR 'cih' OR 'integrative medicine'/de OR 'integrative medicine' OR 'integrative therap*' OR 'complementary therap*' OR 'complementary medicine' OR 'alternative therap*' OR 'alternative medicine' OR ((integrat* OR alternat* OR complement*) NEXT/3 (health* OR therap* OR medicine OR treatment* OR program* OR care OR intervention*))
	#152	Acupuncture	'acupuncture'/exp OR acupuncture OR 'guided imagery'/de OR 'guided imagery' OR 'meditation'/exp OR meditat* OR meditation OR 'massage'/mj OR massag* OR 'progressive muscle relaxation'
	#153	Relaxation	'psychotherapy'/exp/mj OR 'psychosocial care'/de OR 'relaxation training'/de OR 'relaxation therapy':ti,ab OR 'psychotherapy':ti,ab OR psychosocial*:ti,ab OR (relax* NEXT/2 (therap* OR rehab* OR technique* OR train*))
	#154	Mindfulness	'mindfulness based stress reduction'/de OR 'mindfulness based cognitive therapy'/de OR 'mindfulness meditation'/de OR 'mindfulness training'/de OR 'mindfulness based intervention'/de OR 'mindfulness based therapy'/de OR 'mindfulness'/exp OR mindfulness:ti,ab OR 'mindfulness based'
	#155	Yoga/Tai Chi	'tai chi'/mj OR 'tai chi' OR taichi OR 'qigong'/de OR qigong OR 'qi gong' OR 'yoga'/exp OR yoga
	#156	Exercise	(exercise* OR 'physical activity' OR isometric* OR 'weight training' OR (train* NEAR/3 (weight* OR resistance))) AND 'weight lift*' OR 'weight bearing' OR walk* OR run* OR jog* OR swim* OR 'cross train*' OR 'dynamic exercise*' OR aerobics OR ((aerobic OR circuit* OR interval* OR aquatic* OR muscle* OR class OR classes) NEAR/3 (exercis* OR fitness OR training)) OR ((exercise OR (physical NEAR/2 activity)) AND (change* OR improve* OR modif* OR increase*))
	#157	Cognitive Behavioral	'cognitive behavioral therapy'/exp/mj OR 'cognitive behavior* therap*' OR 'cbt' OR 'cognitive behavior*' OR 'rational emotive behavior therapy' OR 'motivational enhancement therapy'/de OR 'motivational enhanc*':ti,ab
	#158	Biofeedback/ Hypnosis	'biofeedback'/exp OR biofeedback OR neurofeedback OR 'hypnosis'/de OR hypnosis OR 'guided imagery'/mj OR 'guide* next/2 imagery'
	#159	Combine Concepts	#149 AND (#150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158)

KQ	Set	Concept	Strategy
KQ 16 (cont.)	#160	Remove Animal Studies	#159 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#161	Remove Pediatric Population	#160 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#162	Remove Unwanted Publication Types	#161 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#163	Limit to Randomized Controlled Trials	#162 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#164	Limit to Meta Analyses and Systematic Reviews	#162 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#165	Combine Concepts	#163 OR #164
	#166	Apply Date Limits	#165 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#167	Limit to English	#165 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim

KQ	Set	Concept	Strategy
KQ 17	#168	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))
	#169	Negative Symptoms/Cognitive Deficits	'anhedonia'/mj OR 'blunted affect'/mj OR 'cognitive defect'/mj OR 'negative syndrome'/mj OR ((cognitiv* NEXT/1 (deficit* OR defect* OR impair* OR symptom*)):ti) OR ((negative* NEXT/1 (affect OR syndrome OR symptom*)):ti) OR anhedonia:ti OR amotivation:ti OR asocial*:ti OR 'blunted affect':ti OR 'poverty of speech':ti
	#170	Selected Neurocognitive Aids	b12:ti,ab OR cyanocobalamin:ti,ab OR 'cyanocobalamin'/de OR cyloserine:ti,ab OR 'cycloserine'/de OR 'd cycloserine':ti,ab OR evista:ti,ab OR folate:ti,ab OR 'folic acid':ti,ab OR 'folic acid'/de OR galantamine:ti,ab OR 'galantamine'/de OR memantine:ti,ab OR 'memantine'/de OR oxytocin:ti,ab OR 'oxytocin'/de OR nmda*:ti,ab OR 'n methyl d aspartate glutamate receptor':ti,ab OR 'n methyl dextro*':ti,ab OR 'n methyl dextro aspartic acid receptor'/de OR raloxifene:ti,ab OR 'raloxifene'/de
	#171	Combine Concepts	#168 AND (#169 OR #170)
	#172	Animal Studies	#171 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#173	Remove Pediatric Population	#172 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Strategy
KQ 17 (cont.)	#174	Remove Unwanted Publication Types	#173 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#175	Limit to Randomized Controlled Trials	#174 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#176	Limit to Meta Analyses and Systematic Reviews	#174 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#177	Combine Concepts	#175 OR #176
	#178	Limit to English	(#175 OR #176) AND [english]/lim
	#179	Apply Date Limits	#178 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
KQ 18	#180	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 18 (cont.)	#181	Collaborative, Team-based Models, Systematic Monitoring, and Patient Engagement Strategies	'body weight loss'/exp OR 'cancer screening'/de OR 'case management'/de OR 'collaborative care team'/exp OR ((care OR team* OR treatment*) NEAR/3 (collaborat* OR communit* OR coordinat* OR integrat* OR interdisciplin* OR model* OR multidisciplin*)) OR (('chronic disease self management' OR harp OR 'health and recovery') NEAR/2 program*) OR 'diet therapy'/de OR 'electronic health record'/de OR 'healthy diet'/de OR 'integrated health care system'/exp OR ((electronic OR interactive OR patient OR health OR medical) NEXT/2 record*) OR ((diet* OR lifestyle OR nutrition*) NEAR/2 (alter* OR change* OR modif* OR intervention*)) OR 'multidisciplinary team'/de OR pact OR 'patient aligned care team' OR 'patient engagement'/exp OR 'patient monitoring'/exp OR ((patient* OR systematic*) NEAR/2 monitor*) OR 'peer group'/de OR (peer* NEAR/2 (counsel* OR lead* OR led OR specialist* OR support*)) OR 'reminder system'/exp OR 'self care'/de OR screen*:ti OR 'smoking cessation'/exp OR team*:ti OR 'vaccination'/de OR 'weight loss program'/de OR 'care team*':ab,ti OR 'case manage*':ab,ti OR ((remind* NEAR/2 (patient* OR system*)):ab,ti) OR ((self NEXT/1 (care OR regulat* OR manag*)):ab,ti) OR 'team based':ab,ti OR 'treatment model*':ab,ti
	#182	Co-occurring General Health Conditions	'bacterial infection'/de OR 'cardiometabolic risk'/exp OR 'chronic disease'/exp OR 'comorbidity'/exp OR ((comorbid* OR 'co occur*' OR general OR multimorbid* OR physical) NEAR/2 (health OR condition* OR disease*)) OR 'diabetes mellitus'/exp OR 'heart disease'/exp OR 'human immunodeficiency virus'/exp OR 'hypertension'/de OR 'lung disease'/exp OR 'malignant neoplasm'/exp OR 'metabolic disorder'/de OR 'metabolic syndrome x'/exp OR 'metabolic syndrome' OR 'muskulokeletal disease' OR 'neurologic disease'/de OR 'nutritional disorder'/de OR 'obesity'/exp OR 'respiratory tract disease'/de OR 'virus infection'/de OR (((atherosclero* OR cardio* OR coronary OR heart) NEXT/2 disease*):ti) OR cancer*:ti OR comorbid*:ti OR 'co occur*':ti OR diabet*:ti OR diet*:ti OR hypertens*:ti OR infect*:ti OR lung*:ti OR metabol*:ti OR multimorbid*:ti OR musculoskeletal:ti OR neurologic*:ti OR nutrition*:ti OR obes*:ti OR pulmonary:ti OR respir*:ti OR weight:ti
	#183	Combine Concepts	#180 AND #181 AND #182
	#184	Remove Animal Studies	#183 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#185	Remove Pediatric Population	#184 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Strategy
KQ 18 (cont.)	#186	Remove Unwanted Publication Types	#185 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#187	Limit to Randomized Controlled Trials	#186 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	#188	Limit to Meta Analyses and Systematic Reviews	#186 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#189	Combine Concepts	#187 OR #188
	#190	Apply Date Limits	#189 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#191	Limit to English	#189 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd AND [english]/lim
KQ 19	#192	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 19 (cont.)	#193	Comorbid Substance Abuse Disorders	'addiction'/de OR 'alcohol abuse'/de OR 'alcoholism'/de OR 'amphetamine dependence'/de OR 'cannabis addiction'/de OR 'cannabis use'/de OR 'cocaine dependence'/de OR 'drug abuse'/de OR 'drug dependence'/de OR 'heroin dependence'/de OR 'inhalant abuse'/de OR 'methamphetamine dependence'/de OR 'opiate addiction'/de OR 'opioid use disorder'/exp OR 'prescription drug misuse'/de OR 'substance abuse'/de OR 'substance use'/de OR 'substance use disorder'/de OR 'tobacco dependence'/de OR 'withdrawal syndrome'/de OR (((alcohol* OR amphetamine* OR benzodiazepine* OR cannabis OR cigarette* OR cocaine OR drug* OR ecstasy OR heroin OR inhalant* OR marijuana OR mdma OR meth OR methadone OR methamphetamine OR narcotic* OR nicotine OR opiate* OR opioid* OR opium OR psychostimulant* OR smoke* OR smoking OR solvent* OR stimulant* OR substance* OR polydrug* OR 'poly drug*') NEAR/3 (abstain* OR abstinen* OR abus* OR addict* OR behavi* OR depend* OR detox* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR user* OR usin* OR utilis* OR utiliz* OR withdraw*)):ti,ab) OR 'co occurring disorder*':ab,ti,kw OR 'dual diagnosis':ab,ti,kw OR ('co occur*' NEXT/5 (condition* OR diagnos* OR disorder*))
	#194	Treatments for Comorbid Substance Abuse Disorders	'alcohol rehabilitation program'/de OR 'alcoholics anonymous'/de OR 'care coordination'/de OR 'case management'/de OR 'clinical decision making'/de OR 'clinical pathway'/de OR 'cognitive behavioral therapy'/de OR 'cognitive remediation therapy'/de OR 'collaborative care team'/de OR 'community based rehabilitation'/de OR 'drug dependence treatment'/de OR 'group therapy'/de OR 'health program'/de OR 'electronic health record'/de OR 'integrated health care system'/de OR 'integrative medicine'/de OR 'interdisciplinary communication'/de OR 'multidisciplinary team'/de OR 'narcotics anonymous'/de OR 'nicotine replacement therapy'/de OR 'peer support'/de OR 'psychosocial care'/de OR 'reminder system'/de OR 'self care'/de OR 'social network'/de OR 'support group'/de OR 'transdermal patch'/de OR '12 step*' OR 'al anon' OR 'al-anon' OR 'community reinforcement' OR meeting* OR 'recovery focused' OR 'support group*' OR 'twelve step*' OR ((alcohol* OR narcotic* OR cocaine*) NEXT/1 anonymous) OR ((case OR contingency) NEXT/1 manag*) OR ((collaborative OR integrat* OR interdisciplin* OR multidisciplin*) NEAR/2 (approach* OR care OR communication* OR health OR intervention* OR medic* OR model* OR program* OR rehab* OR regimen* OR team* OR therap* OR treatment*)) OR ((community OR group* OR peer* OR mutual) NEAR/2 (assist* OR help* OR counsel* OR led OR rehab* OR support* OR therap* OR treatment*)) OR (motivational NEAR/2 (enhancement OR interview* OR therap*)) OR (self NEAR/2 (administer* OR care OR help OR manag*))
	#195	Combine Concepts	#192 AND #193 AND #194
	#196	Remove Animal Studies	#195 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))

KQ	Set	Concept	Strategy
KQ 19 (cont.)	#197	Limit to English	#196 AND [english]/lim
	#198	Remove Pediatric Population	#197 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#199	Remove Unwanted Publication Types	#198 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#200	Limit to Randomized Controlled Trials	'random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab
	#201	Limit to Meta Analyses and Systematic Reviews	('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#202	Combine Concepts	#199 AND (#200 OR #201)
	#203	Apply Date Limits	#202 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
KQ 20	#204	Schizophrenia	'affective psychosis'/de OR 'catatonic schizophrenia'/exp OR 'delusional disorder'/de OR 'depressive psychosis'/de OR 'hebephrenia'/exp OR 'paranoid psychosis'/de OR 'paranoid schizophrenia'/exp OR 'psychosis'/de OR 'schizoaffective psychosis'/exp OR 'schizoidism'/de OR 'schizophrenia'/exp OR 'schizophreniform disorder'/exp OR 'schizophrenia spectrum disorder'/exp OR 'schizotypal personality disorder'/exp OR 'treatment-resistant schizophrenia'/exp OR hebephreni*:ab,ti,kw OR psychoses:ab,ti,kw OR psychosis:ab,ti,kw OR psychotic*:ab,ti,kw OR schizoaffective:ab,ti,kw OR schizofren*:ab,ti,kw OR schizoid*:ab,ti,kw OR schizophasia*:ab,ti,kw OR schizophrenia*:ab,ti,kw OR schizophrenic*:ab,ti,kw OR schizophreniform:ab,ti,kw OR schizotyp*:ab,ti,kw OR (schiz* NOT (schizoc* OR schizod* OR schizog* OR schizok* OR schizol* OR schizom* OR schizon* OR schizope* OR schizophi* OR schizophy* OR schizopo* OR schizosa* OR schizost* OR schizot* OR schizu*))

KQ	Set	Concept	Strategy
KQ 20 (cont.)	#205	Telehealth	'cognitive therapy software'/de OR 'internet'/de OR 'mobile application'/exp OR 'mobile phone'/exp OR 'social media'/de OR 'tablet computer'/de OR 'teleconsultation'/exp OR 'telehealth'/de OR 'telemedicine'/de OR 'telemonitoring'/de OR 'telephone'/de OR 'telepsychiatry'/de OR 'telepsychology'/de OR 'telepsychotherapy'/de OR 'teletherapy'/de OR 'text messaging'/de OR 'video consultation'/de OR 'videoconferencing'/de OR 'web-based intervention'/de OR (((distance OR remote OR tele* OR virtual) NEAR/3 (care OR counsel* OR consult* OR health OR medical OR medicine OR monitor* OR psychiatr* OR psychol* OR psychotherap* OR therapy OR visit*)):ti) OR android*:ti OR app:ti OR apps:ti OR asynchronous*:ti OR automat*:ti OR cellphone*:ti OR 'computer based':ti OR cyber*:ti OR digital:ti OR 'e health*':ti OR ehealth*:ti OR facebook:ti OR facetime:ti OR 'intellispace cognition*':ti OR internet:ti OR ipad:ti OR iphone:ti OR 'lap top*':ti OR laptop*:ti OR 'm health*':ti OR mhealth*:ti OR (((mobil* OR portab*) NEXT/1 (computer* OR device* OR health OR tablet*)):ti) OR 'on line':ti OR online:ti OR phone:ti OR phones:ti OR samsung:ti OR 'short messag* service*':ti OR smartphone*:ti OR (((sms OR text) NEXT/2 messag*):ti) OR ((social NEXT/1 (media OR network* OR platform*)):ti) OR software:ti OR synchronous*:ti OR technolog*:ti OR teleconsult*:ti OR telecounsel*:ti OR telehealth*:ti OR telemed*:ti OR telemonitor*:ti OR telephone*:ti OR telepsych*:ti OR teletherapy:ti OR televisit*:ti OR texting:ti OR video*:ti OR web:ti OR website*:ti OR zoom:ti
	#206	Combine Concepts	#204 AND #205
	#207	Remove Animal Studies	#206 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	#208	Limit to English	#207 AND [english]/lim
	#209	Remove Pediatric Population	#208 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	#210	Remove Unwanted Publication Types	#209 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	#211	Limit to Randomized Controlled Trials	'random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab

KQ	Set	Concept	Strategy
KQ 20 (cont.)	#212	Limit to Meta Analyses and Systematic Reviews	('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	#213	Combine Concepts	#210 AND (#211 OR #212)
	#214	Apply Date Limits	#213 AND [2011-2021]/py AND [1-1-1900]/sd NOT [1-12-2021]/sd
	#215	Combine Results of All KQs	#13 OR #24 OR #35 OR #46 OR #59 OR #70 OR #82 OR #93 OR #104 OR #115 OR #126 OR #137 OR #148 OR #167 OR #179 OR #191 OR #203 OR #214
	#216	Run Retraction Strings	#215 AND ('retraction notice'/de OR retracted:ti OR retraction:ti OR withdrawn:ti)
	#217	Retraction Notices and Original Articles Subject to Retraction	l627204172:id OR l622056935:id OR l619424998:id OR l630167064:id OR l612075562:id OR l612076636:id OR l612244614:id OR l620551293:id OR l361999559:id OR l361705808:id OR l361705810:id OR l361705815:id OR l625060602:id OR l619210902:id OR l358528385:id OR l373088773:id OR l611306993:id OR l610529938:id
	#218	Remove Retracted Materials from Final Set	#215 NOT #217

Appendix J: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Management of FEP and Schizophrenia Algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

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

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: "Individual presenting with suspected psychosis (see **Sidebar 1**)"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Evaluate safety concerns and other urgent needs (see **Sidebar 2**)"
3. Box 2, which connects to Box 3, in the shape of a hexagon, asks, "Are there safety concerns or urgent needs?"
    a. If the answer is "Yes" to Box 3, then Box 4, in the shape of a rectangle: "Refer to mental health or emergency department"
    b. If the answer is "No" to Box 3, then Box 5
4. Box 5, in the shape of a hexagon, asks, "Have diagnoses of a psychotic disorder because of another medical condition and substance/medication-induced psychotic disorder been excluded? (see **Sidebar 3**)"
    a. If the answer is "Yes" to Box 5, then Box 6 in the shape of a rectangle: "Refer to mental health specialty care"
        i. If the answer is "No" to Box 7, then Box 8, in the shape of an oval: "Proceed to **Module B** as appropriate"
    b. If the answer is "No" to Box 5, then Box 7, in the shape of a rectangle: "Complete assessment, treatment, and referrals, as appropriate, including mental health specialty care"

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

1. The algorithm begins with Box 9, in the shape of a rounded rectangle: "Individual with first-episode psychosis or an exacerbation of schizophrenia presents for evaluation/treatment"
2. Box 9, which connects to Box 10, in the shape of a hexagon, asks, "Are there urgent needs?"
    a. If the answer is "Yes" to Box 10, then Box 11, in the shape of an oval: "Consult/treat to address urgent needs (see **Sidebar 2**)"
    b. If the answer is "No" to Box 10, then Box 12

3. Box 12, in the shape of a hexagon, asks, “Is this a first episode of psychosis?”
    a. If the answer is “Yes” to Box 12, then Box 13, in the shape of an oval: “Refer to a coordinated specialty care program for first episode psychosis (see **Sidebar 4**)”
    b. If the answer is “No” to Box 12, then to Box 14
4. Box 14, in the shape of a rectangle: “Conduct clinical evaluation: confirm diagnoses and rule out other conditions (see Sidebar 5), evaluate severity and persistence of symptoms/impairments, identify comorbidities, review history, identify family/other supports, review patient treatment goals. Provide psychoeducation about schizophrenia/psychotic disorder and its treatment.”
5. Box 14 connects to Box 15, in the shape of a rectangle: “Use shared decision making to determine an individualized outpatient treatment plan; consider some or all of the following components: engaging family and peer supports, strategizing for care management/coordinated care (see **Sidebar 6**) and addressing comorbidities (e.g., mental health, substance use, medical), offering psychotherapy/psychosocial treatment (see **Sidebar 6**), offering pharmacotherapy (see **Module C**), monitoring to evaluate treatment of outcomes (see **Sidebar 7**)”
6. Box 15, which connects to Box 16, in the shape of a hexagon, asks, “Are symptoms/impairments severe and/or persistent or have there been multiple previous episodes requiring hospitalization?”
    a. If the answer is “Yes” to Box 16, then Box 17, in the shape of a rectangle: “Consider referral to: Assertive Community Treatment (ACT) or, in VA, Intensive Community Mental Health Recovery services (ICMHR), Residential care programs, or Psychosocial Rehabilitation and Recovery Centers (see **Sidebar 6**)”
    b. If the answer is “No” to Box 16, then Box 18
7. Box 18, in the shape of a hexagon, asks, “Did the individual decline pharmacotherapy?”
    a. If the answer is “Yes” to Box 18, then Box 19, in the shape of a rectangle: “Revisit psychotherapy/psychosocial interventions (see **Sidebar 6**) along with psychoeducation and motivational interviewing”
    b. If the answer is “No” to Box 18, then box 20, in the shape of an oval: “Go to **Module C**”

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

1. The algorithm begins with Box 21, in the shape of a rounded rectangle: "Individual presents with a diagnosis of first-episode psychosis or schizophrenia (from **Module B, Box 20**)"
2. Box 21 connects to Box 22, in the shape of a rectangle: "Initiate/continue psychotherapy/psychosocial interventions (see **Sidebar 6**)"
3. Box 22, which connects to Box 23, in the shape of a hexagon, asks, "Is this an initial treatment of a first episode of psychosis?"
    a. If the answer is "Yes" to Box 23, then Box 25, in the shape of a rectangle: "Using shared decision making, choose antipsychotic medication based on discussion of benefits versus adverse effects; consider starting doses and rates of titration at the lower end of the dose range established for each agent"
        i. Box 25 connects to Box 26
    b. If the answer is "No" to Box 23, then Box 24, in the shape of a rectangle: "Using shared decision making, choose antipsychotic medication, route of administration, and starting dose/ rate of titration based on history of responses, adverse effects, adherence to previous treatment(s), comorbidities, and discussion of benefits versus side effects"
        i. Box 24 connects to Box 26
4. Box 26, in the shape of a rectangle: "Follow-up/reevaluate closely for 4–6 weeks after an initial short-term reevaluation within 1 week (including side effects); allow longer times for comorbid substance use, limited adherence, and slow titration based on aging or medical comorbidities"
5. Box 26, which connects to Box 27, in the shape of a hexagon, asks, "Is there an adequate treatment response?"
    a. If the answer is "Yes" to Box 27, then Box 29, in the shape of a hexagon, asks, "Are there side effects?"
        i. If the answer is "Yes" to Box 29, then Box 30, in the shape of a rectangle: "Manage side effects; consider: Modifying dose, Changing medication(s), Adding other medication directed toward side effects"
            1. Box 30 connects to Box 32
        ii. If the answer is "No" to Box 29, then Box 32, in the shape of a hexagon, asks, "Is there an adequate treatment response?"

b. If the Answer is “No” to Box 27, then Box 28, in the shape of a hexagon, asks, “Is the individual taking the medication as prescribed?”

i. If the answer is “Yes” to Box 28, then Box 29, in the shape of a hexagon, asks, “Are there side effects?”

ii. If the answer is “No” to Box 28, then Box 31, in the shape of a rectangle: “Evaluate causes of non-adherence; address them through education, management of side effects, change to LAI, and psychosocial interventions”

1. Box 31 connects to Box 29

6. Box 30 connects to Box 32, in the shape of a hexagon, asks, “Is there an adequate treatment response?”
7. If the answer is “Yes” to Box 32, then Box 33, in the shape of a rectangle: “Continue treatment with ongoing monitoring of response, side effects, and adherence”
8. Box 33 connects to Box 35
9. If the answer is “No” to Box 32, then Box 34
10. Box 34, in the shape of an oval: “Titrate dose; begin considering a change in medication if there is no response (go to **Box 25**)”
11. Box 35, in the shape of a rectangle: “Evaluate at 3 months; allow longer times for comorbid substance use, limited adherence, and slow titration”
12. Box 35 connects to Box 36, in the shape of an oval: “Go to **Box 37**”
13. Box 36 connects to Box 37, in the shape of a rounded rectangle: “Continued from Box 36”
14. Box 37, which connects to Box 38, in the shape of a hexagon, asks, “Are there significant residual positive or negative symptoms or impairments? (see **Sidebar 6**)”
15. If the answer is “Yes” to Box 38, then Box 39, in the shape of a hexagon, asks, “Have there been adequate trials of adequate dose and duration of at least two antipsychotic medications? (see **Appendix E**)”
16. If the answer is “Yes” to Box 39, then Box 45, in the shape of a rectangle: “Provide psychoeducation about clozapine, begin clozapine treatment, and mitigate risk following clozapine REMS guidelines (see **Sidebar 7**)”
17. If the answer is “No” to Box 39, then Box 40, in the shape of an oval: “Consider change to another antipsychotic medication; go to Box 23”
18. If the answer is “No” to Box 38, then Box 41, in the shape of a hexagon, asks, “Are there significant antipsychotic medication side effects?”

19. If the answer is “Yes” to Box 41, then Box 42, in the shape of a rectangle: “Manage weight gain and metabolic side effects with any combination of diet, exercise, lifestyle interventions, and medication, Manage extrapyramidal symptoms with anticholinergics/other medications, Lower medication dose, if appropriate”
20. Box 42 connects to Box 43
21. If the answer is “No” to Box 41, then Box 43
22. Box 43, in the shape of a rectangle: “Continue current medication with ongoing monitoring of response, side effects, and adherence”
23. Box 43 connects to Box 44, in the shape of an oval: “Consider de-prescribing unnecessary polypharmacy”
24. Box 45, which connects to Box 46, in the shape of a hexagon, asks, “Has there been a response at 4–6 months? (see **Sidebar 6**)”
25. If the answer is “Yes” to Box 46, then Box 47, in the shape of an oval: “Continue treatment plan, follow-up, and adjust as appropriate”
26. If the answer is “Partial response” to Box 46, then Box 48, in the shape of an oval: “Consider augmentation with a second generation antipsychotic or ECT and adjust treatment plan, as appropriate”
27. If the answer is “No response” to Box 46, then Box 49, in the shape of an oval: “Consider changing to another antipsychotic medication to avoid side effects and risks of continued treatment with clozapine, adjust treatment plan, and follow-up, as appropriate”

Appendix K: Abbreviations

Abbreviation	Definition
APA	American Psychiatric Association
APS	Attenuated Psychosis Syndrome
BAC	Balanced accuracy
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CHIME	Connectedness, Hope and Optimism, Identity, Meaning in Life, and Empowerment
CPG	Clinical practice guideline
CSC	Coordinated Specialty Care
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBPWG	Evidence-Based Practice Work Group
EPIC	Early Psychosis Intervention Coordination
EPS-26	Early Psychosis Screener-26
E-RANGE	Enhanced Rural Access Network for Growth Enhancement
FDA	U.S. Food and Drug Administration
FEP	First-episode psychosis
FIDD	Family intervention for dual disorders
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GWAS	Genome-wide association studies
ICD-10	International Classification of Diseases-10
ICMHR	Intensive Community Mental Health Recovery
IMR	Illness Management and Recovery
IOM	Institute of Medicine
iPQ-6	Italian version of the PQ-6
KQ	Key question
MEDD	Morphine equivalent daily dose
MHS	Military Health System
MINI	Mini International Neuropsychiatric Interview
MIRECC	Mental Illness Research, Education, and Clinical Center
MRI	Magnetic resonance imaging
NAM	National Academy of Medicine
NAMI	National Alliance on Mental Illness
NAPLS-2	North American Prodrome Longitudinal 2
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
PANSS	Positive and Negative Syndrome Scale

Abbreviation	Definition
PEPPNET	Psychosis-Risk and Early Psychosis Program Network
PICO(TS)	Population, intervention, comparison, outcome, timing, and setting
PQ	Prodromal Questionnaire
PRIME	Prevention through Risk Identification, Management, and Education
PRONIA	European Personalized Prognostic Tools for Early Psychosis Management
PTSD	Post-traumatic stress disorder
QoL	Quality of Life
RANGE	Rural Access Network for Growth Enhancement
RCT	Randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
ROD	Recent onset depression
SAMHSA	Substance Abuse and Mental Health Services Administration
SANS	Scale for the Assessment of Negative Symptoms
SIPS	Structured Interview for Psychosis-Risk Syndromes
SMI	Serious mental illness
SR	Systematic review
TAU	Treatment as usual
TRRIP	Treatment Response and Resistance in Psychosis
UHR	Ultra-high risk
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VISN	Veterans Integrated Services Network

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