Back to Basics: The Latest on Schizophrenia Spectrum Disorders

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Abstract

Schizophrenia is a chronic psychiatric disorder that has a lifetime prevalence of 1.5 to 3.5 percent of the population and contributes significantly to the global disease burden. A developmental and neurobiological understanding of schizophrenia demonstrates that both genetic and environmental factors, including urbanicity, social fragmentation, and early-life adversity, contribute to illness risk. Comprehensive care that integrates pharmacologic and psychosocial interventions, tailored to individual needs and grounded in hope and recovery, offers the best chance for meaningful, sustained improvement in schizophrenia. Coordinated specialty care, a comprehensive, team-based treatment model for early psychosis, has demonstrated superiority over usual care across multiple domains including symptom reduction, employment and educational attainment, quality of life, and cost-effectiveness. Psychotherapeutic interventions, including cognitive behavioral therapy for psychosis, acceptance and commitment therapy, and family-based models, enhance recovery, functioning, and quality of life. Digital and community-based approaches offer promising opportunities for outreach and engagement. Antipsychotic medications—including clozapine as a unique and underutilized treatment, newer medications, and long-acting antipsychotics—remain an important tool for many individuals with schizophrenia. Systematic monitoring of metabolic, neurologic, cardiovascular, and endocrine/reproductive side effects should occur. This paper provides important information regarding creating and improving services for individuals with schizophrenia and ways to foster recovery. It includes an overview of the prevalence, risk factors, treatment approaches, and opportunities for prevention. This information can help state policymakers, behavioral health system leaders, people with lived experience, providers, and others develop services that can more effectively address the needs of people with schizophrenia and related conditions.

Highlights

- Childhood exposure to socially fragmented environments is associated with brain changes and maladaptive beliefs that may increase risk for developing psychosis later in life.
- Shortening the duration of untreated psychosis is critical because earlier treatment initiation is consistently associated with better long-term clinical and functional outcomes.
- Psychotherapy offers numerous evidence-based approaches that can be integrated and modified to support recovery. Cognitive behavioral therapy for psychosis is the most used, with new complementary and expanded approaches emerging.
- Multi-element, team-based coordinated specialty care is the gold standard of early psychosis care.
- Despite being the most effective treatment for treatment-resistant schizophrenia, clozapine remains underutilized in the United States.
- Long-acting injectable antipsychotics reduce relapse, hospitalization, and mortality rates and should be offered early in the illness if the individual in care prefers them or if medication adherence is low.

Recommendations[1]

1. Optimal schizophrenia care requires coordinated pharmacologic and psychosocial treatments. Systems should be structured to deliver both components.
2. Proactive efforts to identify individuals with early schizophrenia and engage them in coordinated specialty care (CSC) should be initiated because evidence shows that clinical improvements are much greater when CSC is delivered early in the course of illness.
3. Psychotherapy should be considered for every individual experiencing psychosis, irrespective of acuity and setting. Psychotherapy should be offered in multiple modalities (e.g., individual, group, and family) to ensure a comprehensive approach to recovery. The significance of family therapy and family support in recovery should be highlighted at the start of treatment.
4. Antipsychotic medications should be prescribed at the lowest effective dose required to facilitate meaningful recovery. Continuous antipsychotic treatment should be continued in multi-episode schizophrenia to minimize medical morbidity, reduce the risk of psychiatric hospitalization, and prevent mortality.
5. Clozapine should be considered after two failed antipsychotic trials. Systems should implement decision-support tools and workflows to help clinicians identify treatment-resistant schizophrenia.
6. Clinicians should proactively address adherence by engaging natural supports, offering shared decision-making, and routinely monitoring for medication effectiveness and side effects.
7. Long-acting injectable antipsychotics should be presented as a routine, proactive option, particularly in early schizophrenia, to promote adherence and prevent relapse.

[1] These recommendations and the information in this paper do not constitute individual medical advice. People in care should consult with their physician and treatment providers.

Introduction

Schizophrenia and other psychotic disorders are among the most disabling mental illnesses globally, with a lifetime prevalence in the population of 1.5 to 3.5 percent.[1] In 2019, the economic burden of schizophrenia in the United States alone was estimated at $343.2 billion.[2] Schizophrenia is a serious mental illness that affects how individuals think, feel, and behave. It is characterized by persistent psychosis lasting 6 months or more, during which individuals lose touch with reality.[3] This can be deeply distressing for both the affected individuals and their loved ones.

Core symptoms of schizophrenia include hallucinations, delusions (i.e., false fixed beliefs), and disorganized thinking. Individuals often experience reduced emotional expression, lack of motivation, social withdrawal, motor difficulties, and cognitive impairments (often referred to as *negative symptoms;* **Figure 1**).[4] The disorder typically emerges in late adolescence to early adulthood, with males generally affected earlier (late teens to early 20s) than females (early 20s to early 30s).[5] The onset of psychosis is referred to as first-episode psychosis, which affects approximately 122,000 individuals annually in the United States.[6,7]

Early intervention during first-episode psychosis is crucial for improving long-term outcomes. With timely mental health care and social support, many individuals can lead fulfilling and productive lives. Without appropriate treatment, however, they may face lifelong health and socioeconomic challenges. Subtle cognitive and social changes often precede a formal diagnosis by several years. Although symptoms usually begin in adolescence or early adulthood, schizophrenia is increasingly understood from a developmental perspective.[8] Early signs of the disorder include cognitive delays or unusual behaviors that may appear in childhood, suggesting that the disorder may stem from disruptions in brain development and environmental stressors, including in the prenatal time period, or as a result of early-life adversity.[8] This developmental view supports the importance of early detection and intervention.

One area of focus is identifying individuals at clinical high risk for psychosis (CHR-P).[9] These individuals exhibit early warning signs such as attenuated psychotic symptoms or brief intermittent psychotic episodes. They also can be identified through a combination of genetic risk and functional decline. The prevalence of CHR-P is estimated at around 4 percent,[10] with 20 to 30 percent of these individuals eventually transitioning to complete psychosis within 2 to 3 years.[11] Another related concept is psychotic-like experiences (PLEs), which are subthreshold hallucinations or delusions. These experiences are relatively common in the general population, with prevalence estimates ranging from 8 to 17 percent.[12] Although most PLEs are transient and benign, persistent and distressing PLEs are linked to a higher risk of developing psychotic disorders.[13] Understanding the prevalence and characteristics of schizophrenia and related psychotic spectrum disorders across different stages and populations enables the development of effective strategies for early detection, intervention, and long-term support. This can improve outcomes for those at risk for or affected by psychosis.

Figure 1: Key Terminology

Psychosis is defined as a loss of touch with, or disconnection from, reality due to a disruption in how the brain processes information. During an episode of psychosis, a person may have difficulty distinguishing what is real from what is not. Psychosis can occur as a symptom of schizophrenia spectrum disorder, mania, depression, or certain medical conditions (such as infections or autoimmune disorders), or it may be caused or worsened by some substances like cannabis or psychostimulants.

Schizophrenia† is a mental illness characterized by psychosis that affects how a person thinks, feels, and behaves. People with schizophrenia may experience positive, negative, cognitive, and disorganized symptoms (see definitions below). These symptoms typically last at least 6 months, and the earliest signs often appear in the late teens or twenties. It is a heterogeneous condition, meaning it can look different from person to person, with a variable course and outcome. Schizophrenia is commonly misunderstood and is sometimes mistaken for other conditions, such as multiple personality disorder. Some people with schizophrenia may lack awareness or insight of the symptoms they are experiencing. Schizophrenia can cause a significant impact on a person's functioning, but with treatment and support, people can live meaningful lives.

Schizoaffective disorder† is a mental illness in which a person experiences both symptoms of a mood disorder (major depression or mania) and symptoms of schizophrenia. Symptoms of a mood disorder must be present for the majority of the period of active illness, and there must be at least a 2-week period when delusions or hallucinations occur in the absence of a mood episode.

Schizophrenia spectrum disorder is a continuum of mental health disorders that includes schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, and schizotypal personality disorder. These disorders share the core symptom of psychosis but differ in duration and severity.

Positive symptoms include hallucinations (such as hearing voices or seeing things that are not there), paranoia, and exaggerated or distorted perceptions, beliefs, and behaviors.

Negative symptoms include reduced emotional expression (affective flattening), decreased speech output (alogia), reduced desire for social contact (asociality), reduced drive to initiate

and persist in purposeful activities (avolition), and decreased experience of pleasure (anhedonia).

Disorganized symptoms include disruptions in thought and behavior that make it difficult to organize thoughts, communicate clearly, or complete daily tasks. This may include disorganized speech, unusual movements, and unpredictable or inappropriate emotional responses.

Adapted from: https://www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia

† *Full criteria can be found at: American Psychiatric Association.* Diagnostic and Statistical Manual of Mental Disorders. DSM-5-TR. *American Psychiatric Association Publishing; 2022. doi:10.1176/appi.books.9780890425787*

RISK FACTORS AND ETIOLOGY

Although the exact causes of schizophrenia are largely unknown, research has shown that a combination of genetic and environmental factors increases the risk for schizophrenia and associated psychotic disorders. There is not a single or small number of inherited genes that would directly lead to psychosis. Rather, genome-wide association studies reveal that multiple genes may have small effects to influence psychosis risk.[14] Heritability estimates for schizophrenia have often been quoted as 60 to 80 percent, but the studies that yield that data have failed to account for gene–environment correlations or interactions.[15,16]

It has long been known that environmental factors affect psychosis risk beginning in the prenatal period, aligning with the neurodevelopmental hypothesis of schizophrenia. A recent review and meta-analysis identified several prenatal and perinatal factors that were associated with a later onset of psychosis.[17] These include paternal age younger than 20 and older than 35, maternal infections, nutritional deficits in pregnancy, maternal hypertension, hypoxia, and obstetric complications. Positive maternal mental health as well as physical health are critical to help mitigate some of these risks.

For more on maternal mental health, see another paper in the FY2025 Technical Assistance Coalition series, "Improving Maternal Mental Health in Women with Serious Mental Illness."

Beyond the prenatal environment, burgeoning research on the environment post-birth has shed light on neighborhood-level or area-level risk factors.[8] Neighborhood characteristics are derived from publicly available sources linked to a participant's address and zip code. They measure a variety of environmental factors, including air pollutants and aggregated surveys from thousands of residents within a catchment area. As a result, neighborhood characteristics provide an objective measure of the environment and are less likely to be influenced by recall bias as in other methodological approaches.

It has long been known that urban upbringing (i.e., growing up in cities during childhood) is a major risk factor for developing psychosis later on in life.[18] This association has been mediated,

in part, by area-level social fragmentation.[19] Social fragmentation is characterized by the disruption of social ties and relationships among residents and families in communities.[20] Neighborhood social fragmentation is measured by residential instability (the percentage of residents who changed addresses in the past year), the percentage of renter-occupied housing, the percentage of residents who live alone, the percentage of unmarried residents, and the percentage of single-parent households.[18] Indices of social fragmentation have been shown to be associated with greater schizophrenia rates,[18] earlier age of psychosis onset,[21] conversion to psychosis among youth at CHR-P,[22] and distressing PLEs.[23] The social disorganization theory posits that in socially fragmented neighborhoods, the lack of a stable social environment and the absence of collective efficacy in norms lead people to feel a sense of isolation, social exclusion, and a lack of belonging, which can be particularly negative to children's mental health.[24]

Recent research has started to shed light on the possible psychological and biological mechanisms of how the social environment may lead to psychosis. Many of these studies have been conducted using large data sets such as the North American Prodrome Longitudinal Study (NAPLS) and the Adolescent Brain Cognitive Development (ABCD) Study. NAPLS is a multi-site study focused on identifying biomarkers and mechanisms of how CHR-P youth transition to psychosis. ABCD is a nationally representative cohort of more than 11,000 children who were followed for 10 years. The results of one NAPLS study suggests youth who grew up in areas with greater social fragmentation experienced greater lifetime perceived discrimination, which, in turn, led to more maladaptive core schemas in adulthood.[25] These findings suggest that a lack of stable social relationships during childhood may lead to self-defeating beliefs and patterns of thinking, feeling, and behaving. These pervasive patterns of maladaptive beliefs have been implicated in the development and persistence of psychosis.[26] Perhaps the stress from unmet emotional needs from an early age may also adversely affect neurodevelopment.

Core schemas are fundamental beliefs about oneself, others, and the world. They are deeply ingrained and resistant to change without targeted intervention.

Recent research has demonstrated that having lived in areas with greater social fragmentation during childhood is linked with reduced grey matter volume in brain regions implicated in psychotic disorders, including the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, and the hippocampus.[27] These brain regions are critical for complex social interactions as well as a range of cognitive and emotional processes that are often compromised in psychotic disorders,[28,29] including executive function,[30,31] emotional regulation and conflict monitoring,[32] and detection of discrepancies between expectations informed by stored memories and incoming sensory data.[33] The connectivity between the hippocampus and temporoparietal regions of the brain has also been shown to be specifically deviant among youth at CHR-P who live in socially fragmented neighborhoods.[34] In addition, youth at CHR-P living in neighborhoods with greater social fragmentation exhibit greater mismatch negativity (i.e., deviations in electrical activity in the brain in response to an odd stimulus in a sequence of stimuli), which is specifically linked to poorer social functioning and schizophrenia.[35] While other research has demonstrated these neural biomarkers to be predictive of psychosis,[36] recent research on neighborhood characteristics points toward a possible etiology of one's social environment that may lead to these neural deficits seen in psychosis.[18,37]

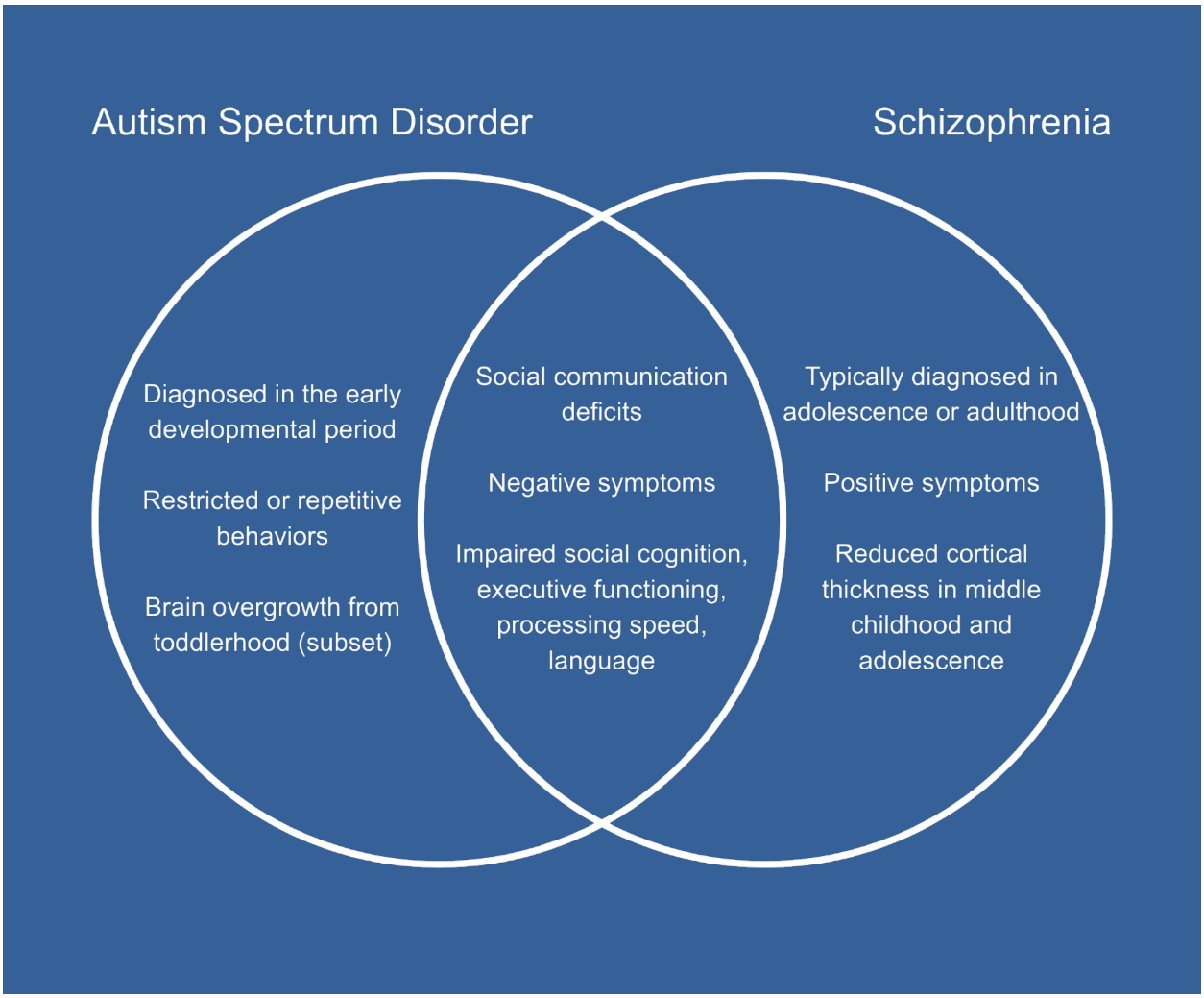
Another line of evidence supporting the important role of the social environment in psychosis involves the study of gene-environment interaction. In ABCD, researchers found that the polygenic scores for schizophrenia predicted persistent (but not transient) symptoms of distressing PLEs among children over 4 years.[38] However, this genetic effect was attenuated by greater involvement in physical activities, as measured by their participation in sports. In other words, among those who were more engaged with sports, their genetic score no longer conferred a risk of developing PLEs, but among those who were less engaged with sports, their genetic score predicted the development of PLEs much more significantly. In fact, team sports (as opposed to individual sports) mainly explained the protective effect of physical activities on persistent distressing PLEs, particularly against the genetic risk for schizophrenia. Perhaps the social components of being part of a team play an important role in offsetting the risk of psychosis. Although reciprocally, it may be difficult to disentangle whether youth at high risk are less likely to participate in team sports due to early negative symptoms or social withdrawal. Altogether, evidence from different disciplines, ranging from public health, neuroscience, and genetics, converges on the important role of the social environment in the development of psychosis.

CONSIDERATIONS FOR CHILDREN AND ADOLESCENTS

A person with a serious emotional disturbance, or SED, is defined as a person less than 18 years old with a "diagnosable, mental, behavioral, or emotional disorder that resulted in functional impairment that substantially interferes or limits the child's role in functioning in family, school, or community activities."[39] A range of psychiatric diagnoses can qualify as an SED, depending on their severity and functional impact. Examples include major depressive disorder, bipolar disorder, anxiety disorders, post-traumatic stress disorder, psychotic disorders, and others.

Schizophrenia is rare in children and can be divided into (1) early-onset schizophrenia, with an age of onset prior to age 18, and (2) childhood-onset schizophrenia, with an age of onset prior to 13.[40] The incidence of childhood-onset schizophrenia is less than 0.04 percent.[41] The presence of positive symptoms of psychosis in a child does not necessarily indicate an underlying diagnosis of schizophrenia, and clinicians should consider a wide differential diagnosis of psychiatric and medical conditions. Childhood schizophrenia should also be differentiated from autism spectrum disorder, which can share overlapping features, including social withdrawal and unusual behaviors. Differentiating schizophrenia from autism spectrum disorder is discussed in more detail in **Figure 2.**

Figure 2: Differentiating Autism Spectrum Disorder from Schizophrenia



—Adapted from Jutla A, Foss-Feig J, Veenstra-VanderWeele J. Autism spectrum disorder and schizophrenia: an updated conceptual review. Autism Res. *2022;15(3):384-412. doi:10.1002/aur.2659*

Early schizophrenia care and identification

EVIDENCE-BASED TREATMENT FOR EARLY SCHIZOPHRENIA

More than 100,000 people experience a first episode of schizophrenia or related psychotic disorder in the United States each year.[6] Historically, care for young people in the early phase of schizophrenia involved treatment delays of 1 to 3 years or longer, was fragmented, and was focused mainly on stabilizing symptoms as opposed to recovery or participation in work, school, or relationships.[42,43] These young people commonly lived lives of substantial long-term disability, social isolation, and limited work and school opportunities.

NATIONAL INSTITUTE OF MENTAL HEALTH RECOVERY AFTER AN INITIAL SCHIZOPHRENIA EPISODE INITIATIVE

Recognizing the urgent need for more effective care for young people with early schizophrenia, the National Institute of Mental Health (NIMH) launched the Recovery After an Initial Schizophrenia Episode (RAISE) research initiative in 2008. RAISE aimed to fundamentally alter the trajectory and prognosis of schizophrenia through coordinated and aggressive treatment in the earliest stages of illness.

Through the research and clinical programs developed in other countries, it was established that specialized early schizophrenia services produced superior outcomes compared with standard care: rapid remission of positive symptoms, fewer relapses, less hospitalization, better functioning, and improved quality of life.[44] NIMH sought these recovery-oriented outcomes for young people with schizophrenia in the United States.

RAISE tested a specialized, multi-element, team-based approach to early schizophrenia called coordinated specialty care (CSC). Within RAISE, NIMH funded both a clinical trial of CSC—the RAISE Early Treatment Program (RAISE-ETP)—and the complementary RAISE Connection Program, which developed practice tools for broad implementation of CSC programs in the U.S. healthcare context. Together, RAISE studies involved 22 states, 36 community clinics, 134 clinicians, and 469 participants. NIMH also funded the Specialized Treatment Early in Psychosis (STEP) trial, testing CSC in community health centers.

COORDINATED SPECIALTY CARE: AN INTEGRATED TEAM-BASED APPROACH

In a CSC program, a team of clinicians works with each individual in care to develop a personalized treatment plan. They focus on recovery, work and school participation, family support, and appropriate medications to help the young person get their life back on track. The specific treatment components, delivered in an integrated fashion, include the following evidence-based interventions for early schizophrenia:[45]

- Psychiatric assessment and medication
- Cognitive and behavioral psychotherapy
- Family education and support
- Supported employment and education
- Assertive case management

Led by a dedicated team leader, CSC programs are imbued with *hopefulness for the future of the person receiving care* and the *belief that recovery is possible for everyone.* This recovery orientation represents a transformation in schizophrenia care. CSC is *person centered;* services are delivered in support of the treatment goals of the person receiving services, and that person is free to choose which services to use.

Shared decision-making is the framework for making personalized CSC treatment decisions. The individual in care and clinicians discuss treatment options in terms of the individual's goals, the treatment risks and benefits, and any alternatives to the proposed treatment. CSC's shared

decision-making framework gives the person receiving services equal voice and represents another departure from conventional schizophrenia care.

Finally, CSC is distinguished from routine early schizophrenia care in its proactive outreach to identify individuals experiencing early schizophrenia and engage them in care. This early intervention strategy contrasts with conventional care that typically treats such individuals only when they find their way to a clinic or are hospitalized. CSC strives to intervene as early as possible in a first episode of schizophrenia, when the likelihood of recovery is greatest and before the individual is in crisis.

> "CSC is truly unique. It offers all of the essential supports that a young person experiencing early psychosis needs under one umbrella and weaves them together in a way that reflects that young person's life and goals. It encourages family members to participate in learning not just about psychosis but also recovery and shows them how they can be instrumental in that journey for their loved one and themselves. She finished high school and started community college. She began rebuilding her sense of self and agency. We will be forever grateful to CSC for helping our daughter find herself again and want to not just survive but thrive."
>
> —Bonnie, parent of CSC service user in California

RAISE FINDINGS AND EVIDENCE FOR CSC

In both rigorous clinical trials and community-based evaluations of CSC, CSC produced substantial clinical improvements across a range of outcomes valued by individuals with early schizophrenia and their families:

- The RAISE-ETP clinical trial found that after two years of treatment, CSC was superior to usual community care for early schizophrenia; individuals had greater improvements in quality of life, symptom improvement, and involvement in work or school.[46] CSC was also more cost-effective than early schizophrenia care typically available in communities.[47]
- Participation in the RAISE Connection Program was associated with greater improvements in symptoms and functioning, with participants more likely to remain engaged in the CSC program than is typical for early schizophrenia care.[48]
- In the STEP clinical trial, individuals receiving CSC services had fewer psychiatric hospitalizations and were more likely to be employed or in school than those in standard care for early schizophrenia.[49]
- In an evaluation of the New York statewide OnTrackNY CSC program involving 325 individuals in care, which operated without research support, education and employment rates doubled from 40 to 80 percent by 6 months of participation in the program; hospitalization rates dramatically decreased from 70 to 10 percent within 3 months; and symptoms and social and occupational functioning improved over 12 months. The greatest gains occurred in the first 3 months of CSC and continued over time.[50]

- In a study of 770 individuals with early schizophrenia in 36 community CSC programs in 22 states, CSC programs with greater *fidelity to the core CSC components* produced greater improvements for people receiving services.[51]
- Finally, in a meta-analysis of 10 clinical trials of specialized early intervention services for early schizophrenia, the specialized services were associated with better clinical outcomes across all outcomes examined, including decreased psychiatric hospitalization, greater involvement in work or school, and reduced symptom severity.[52]

CSC is now the gold standard of early schizophrenia care. As a broad consensus on the superiority of CSC for early schizophrenia emerged, CSC increasingly became available in communities across the United States. Consequently, in its *2020 Practice Guideline for the Treatment of Patients with Schizophrenia*, the American Psychiatric Association (APA) recommended that individuals experiencing a first episode of schizophrenia be treated in a CSC program.[53]

> "It felt like I was trapped in a nightmare. . . . Without this program my life would look so different. I am currently attending college full-time as well as working around 20 hours a week. My life is normal again. I no longer think people are following me. I no longer believe people can hear my thoughts. I can comprehend time again. . . . This program saved my life."
>
> —Avi, a CSC service user in Minnesota

In sum, specialized early intervention for schizophrenia in the form of CSC is more effective than usual care and can be feasibly delivered and brought to scale in the United States. RAISE likewise accomplished its central goal of producing clinically meaningful and actionable findings that could be translated rapidly into practice.

NATIONWIDE EXPANSION OF CSC

Moving effective treatment into practice requires more than compelling research findings; the annals of mental health literature document legions of interventions with ample evidence of effectiveness that have never moved outside the research lab. In this section, factors that fueled the rapid expansion of CSC programs in the United States and the status of CSC programs today are examined.

CSC's rapid uptake across the United States results from a combination of factors: (1) CSC study designs built to facilitate CSC implementation, (2) production of compelling evidence for CSC's effectiveness, (3) partnerships with key CSC stakeholders, and (4) investment in CSC infrastructure and training.

The RAISE studies were designed to support broad uptake of CSC across the United States. While the rigorous RAISE-ETP clinical trial produced clear evidence of CSC's effectiveness, the RAISE Connection study also produced a suite of sharable practice tools to support planning and implementation of CSC treatment programs, including interactive tools to estimate the costs and resources to start a CSC program,[54] practical methods for monitoring fidelity of the program to the evidence-based CSC model,[55] and other resources to guide CSC program

implementation.[48] Likewise, the RAISE studies relied on existing community clinics and clinicians to deliver CSC, providing insights on how to train providers and implement CSC in typical mental health agencies.

NIMH also formed partnerships with entities instrumental in early schizophrenia care, such as mental health advocacy groups, funders, federal partners, provider organizations, and local and state mental health authorities. These stakeholders provided critical input on outcomes they saw as most valuable, financing of CSC services, and integration of CSC into the healthcare landscape in the United States. Consequently, when CSC was demonstrated effective, these partners championed CSC because it aligned with their needs and goals.

The collaborations NIMH formed among early schizophrenia stakeholders, coupled with RAISE's clinically meaningful and actionable findings, created the momentum for new federal and state investments in CSC services, transforming early schizophrenia care across the United States.[56] From 2014 to 2025, the Mental Health Block Grant set-aside program has required that every U.S. state and territory provide treatment for first-episode psychosis. This has played a significant role in funding CSC programs.[57]

The proliferation of CSC programs created an opportunity to further advance early schizophrenia care, recovery, and scientific discovery, and NIMH established the Early Psychosis Intervention Network (EPINET) in 2019. A national early schizophrenia learning healthcare partnership, EPINET links more than 100 CSC clinics in 17 states to conduct continuous quality improvement of CSC services and practice-oriented research.[58]

In 2008, only a few community treatment programs in two states offered specialized care for early schizophrenia. Now all 50 states have CSC programs, and tens of thousands of young people with early schizophrenia receive CSC in nearly 400 CSC programs. Individuals seeking CSC can access the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Early Serious Mental Illness Treatment Locator at https://www.samhsa.gov/find-help/locators/esmi to find a program near them.

> "Coordinated specialty care is an important evolution in early schizophrenia services. Robust and recovery-oriented, CSC services are embedded in a primary foundation of hope and the belief that everyone can recover. The marriage of research, clinical support, state and federal funding, and the support of family and other advocacy organizations—these all contributed to the broad uptake of CSC in this country and investment in our young people."
>
> —Dr. Lisa Dixon, principal investigator of the NIMH-sponsored RAISE Connection Program trial; leader of OnTrackNY, a network of CSC programs across New York State; and professor of psychiatry, Columbia University Medical Center

CHALLENGES

Despite CSC's science-to-service success story, challenges persist in delivering high-quality early schizophrenia care, such as these:[59]

- strengthening the business model for funding CSC in the private and public sectors
- need for frequent CSC staff training due to high staff turnover
- speeding access to care
- organizing services to support long-term recovery for persons transitioning out of CSC
- eliminating differences in care experienced by different populations

EARLY IDENTIFICATION AND TREATMENT ENGAGEMENT

TIMING MATTERS

While CSC is the gold standard treatment for early schizophrenia, timing matters. In the RAISE-ETP trial, clinical improvements were much greater when CSC was delivered closer to the onset of illness.[5] Longer *duration of untreated psychosis (DUP)*, the time between onset of psychosis (a central feature of schizophrenia) and initiation of appropriate treatment, is strongly associated with poor outcomes across numerous studies.[60] The early phase of schizophrenia represents a critical opportunity to intervene and alter the downward trajectory and poor outcomes historically associated with schizophrenia. Hence, timely identification of early schizophrenia and engagement in care are crucial to streamlining the pathway to care, reducing DUP, and achieving optimal treatment outcomes.

RECOGNIZING EARLY SCHIZOPHRENIA SYMPTOMS

Although CSC programs may enroll people following a psychiatric hospitalization, they'll ideally identify and connect with individuals before they are in crisis. Educating outpatient mental health clinicians and primary care providers, emergency room staff, and juvenile justice and correctional mental health professionals on early schizophrenia and facilitating connection to CSC programs can shorten DUP.

Recognizing early symptoms of schizophrenia as such is the first step in identifying individuals who may benefit from CSC. Yet doing so is challenging even for seasoned mental health clinicians, who may have little experience with this population. Perhaps surprisingly, individuals with early schizophrenia who are already in mental health care often experience substantial delays between illness onset and initiation of treatment for schizophrenia. Hence, mental health professionals might reduce DUP among help-seeking individuals by adopting systematic procedures for early schizophrenia screening, followed by thorough diagnostic assessment for positive screens and engagement in CSC for those diagnosed with early schizophrenia. The Prodromal Questionnaire—Brief Version (PQ-B) is the most used brief screener for early schizophrenia and those at clinical high risk of schizophrenia.[61] It is appropriate for use in clinical settings, including mental health clinics, and is available in numerous languages.

INTERNET AND SOCIAL MEDIA PLATFORMS

Many young people with early schizophrenia have only infrequent contact with healthcare professionals. In general young people spend more time on the internet and social media compared with the rest of the population, which presents a huge opportunity to reach young people (and their families) early in their illness as they anonymously seek mental health information and treatment options. Dr. Michael Birnbaum, medical director of OnTrackNY, a network of CSC programs in New York State, has found that young people are more likely to search online for information and help than discuss their concerns with peers, family, or

clinicians.[62] He is pioneering the use of social media platforms to educate help seekers on early schizophrenia, identify those needing care, and engage them in a CSC program.

MEETING YOUNG PEOPLE AND FAMILIES WHERE THEY ARE

Critical to reaching individuals with early schizophrenia and their families is using language that speaks to them and their experiences, rather than clinically correct but unfamiliar and sometimes frightening terms like "delusions" or "psychosis." For example, the OnTrackNY website[63] reads as follows:

> OnTrackNY is a network of innovative mental health treatment programs for teens and young adults across New York State who have recently had unusual thoughts, behaviors, or perceptions (like seeing things that others don't).

There is no single way to reach all individuals with early schizophrenia. Accordingly, Dr. Vinod Srihari, who directs the STEP CSC program, conducted a large clinical trial aimed at reducing lengthy DUP within an entire catchment area using multiple messaging channels and approaches.[64] Over 4 years, the MindMap campaign targeted various sources of treatment delay for early schizophrenia using public education via mass and social media, professional outreach and detailing, and rapid enrollment of referrals to CSC. This complex intervention, which succeeded in progressively reducing DUP and increasing referrals to CSC, also demonstrated that such campaigns take time—often years—to work.

CSC programs attempting to minimize DUP target the settings that young people and their families frequent, including schools, places of worship, and jails, tailoring their messaging to the audience and communicating often. Above all, across audiences and settings, CSC programs communicate a sense of hope that recovery is possible.

CLINICAL HIGH RISK FOR PSYCHOSIS

Individuals with CHR-P are symptomatic, functionally impaired, and at high risk for developing an overt psychotic disorder, most often a schizophrenia spectrum disorder. Proactively identifying and treating people with CHR-P represents a paradigm shift in early intervention. Should the individual with CHR-P convert to a psychotic disorder, they can immediately be referred to CSC, nearly eliminating the DUP entirely.

In the United States, clinicians most often screen for CHR-P using the PQ-B in conjunction with early schizophrenia screening. A positive PQ-B screen is followed by a diagnostic interview, most commonly the Structured Interview for Psychosis-Risk Syndromes (SIPS). While specialized CHR-P treatment programs are limited in the United States, various treatment modalities, especially cognitive behavioral therapy, appear promising in reducing conversion to a psychotic disorder.

ALTERNATIVES TO CSC

The effectiveness of CSC for early schizophrenia is now well established, but clinicians still lack data on what represent the "active ingredients" of CSC. It is not yet known whether all CSC elements, in combination, contribute to CSC's beneficial outcomes or whether certain CSC elements contribute uniquely to specific outcomes.

What can clinics offer individuals with early schizophrenia that might enhance their recovery when program resources are limited? The substantial body of evidence for CSC's effectiveness rests on implementation of the *full CSC model.* However, based on lessons learned since the 2008 launch of RAISE, incorporating certain CSC program features into care for individuals with early schizophrenia might be considered, either individually or in combination, including the following:

- **recovery orientation** to imbue treatment with hope and the belief that recovery is possible
- **shared decision-making framework** for making personalized treatment decisions
- **person-centered services framework** where services are delivered in support of the individual's treatment goals, and the individual is free to choose which services to use
- **peer support and peer-delivered services,** which show that recovery is possible
- **supported employment and education services,** often the only treatment individuals initially want, as it meets their immediate goal of returning to work or school
- **team meetings** among a person's providers to support integrated care
- **team leader** for early schizophrenia services to reduce service fragmentation
- **case management** to support linkage to needed outside services—for example, supported employment
- **systematic measurement** of schizophrenia symptoms and medication side effects

Psychosocial interventions

Psychotherapy for people with schizophrenia has seen an increase in research and practice following decades of belief that individuals living with schizophrenia could not participate in therapy, experience meaningful change in their experience, or achieve recovery (**Figure 3**). This welcome shift has ushered in new therapeutic approaches and the refinement of existing evidence-based orientations to support people living with schizophrenia toward recovery. The current landscape includes individual, family, and group approaches as well as programmatic models of care that emphasize the recovery model with intentional consideration for peer-led service models and community support.

Figure 3: Working Definition of Recovery

***Recovery* can be defined as a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential.**

The 10 guiding principles of recovery are as follows:

- Hope: Belief that recovery is possible
- Person-driven: Individuals set their own goals and pathways
- Many pathways: Recovery is unique and can take multiple forms
- Holistic: Addresses the whole person—mind, body, spirit, and community
- Peer support: Encouragement from others with lived experience
- Relational: Supportive relationships are central
- Culture: Values and traditions shape recovery
- Addresses trauma: Recognizes and responds to the impact of trauma
- Strengths and responsibilities: Builds on personal strengths while fostering accountability
- Respect: Upholds dignity, rights, and inclusion

—Adapted from SAMHSA's Working Definition of Recovery | SAMHSA Library. Accessed July 30, 2025. https://library.samhsa.gov/product/samhsas-working-definition-recovery/pep12-recdef

The recommended model of care is one that emphasizes an integrated, tailored approach using evidenced-based approaches with adjunctive interventions that enhance personal fit. This framework is consistent with recent work highlighting the factors that influence subjective experience of effective psychotherapy for schizophrenia: flexibility, therapeutic alliance, and other salient features (e.g., expressive therapies such as music therapy).[65] Moreover, expanding outcomes to be inclusive of domains such as well-being and identity formation also demonstrates effectiveness when combined with traditional approaches.[66,67] This section provides an overview of the current approaches to psychotherapeutic intervention, including complementary models.

INDIVIDUAL PSYCHOTHERAPY APPROACHES

For a summary of individual psychotherapy approaches, please refer to **Table 1.**

COGNITIVE APPROACHES TO PSYCHOSIS

Cognitive psychotherapy approaches represent a diverse array of theoretical perspectives. They inform a family of therapeutic styles, and they are distinct in their structured nature, largely focusing on symptom monitoring and reduction. Strategies aim to identify problematic thought processes and develop alternative cognitions, thereby influencing emotional and behavioral responses. Critical components include behavioral activation, psychoeducation about cognitive distortions and thinking errors, guided interventions and skills training, and relapse prevention.[68,69]

Cognitive behavioral therapy for psychosis (CBTp) is the most recommended psychotherapy approach for individuals living with schizophrenia with the most evidence for effectiveness.[70] CBTp has been shown to reduce positive symptoms of psychosis through restructuring intrusive thoughts about sensory experiences and false belief systems toward more evidenced-based cognitions.[56] Behavioral activation and regulatory approaches aim to improve engagement with meaningful behaviors. CBTp is developed for early intervention and medication-resistant care,[59] and it has been adapted across clinical settings (e.g., inpatient and outpatient) and for group and family formats.[71] Recovery-oriented cognitive therapy (CT-R) is an extension of CBTp that includes recovery elements such as hope, empowerment, and purpose cultivated through activities and interpersonal connection. CT-R has demonstrated benefits for symptom improvement and overall functioning.[72,73]

ACCEPTANCE AND COMMITMENT THERAPY FOR PSYCHOSIS AND MINDFULNESS-BASED THERAPIES

Acceptance and commitment therapy (ACT) and mindfulness-based therapies are psychotherapy approaches directly informed by their cognitive predecessors. These approaches focus on nonjudgmental present-moment awareness, acceptance, compassion, and intentional and valued actions.[74,75,76,77,78] The overarching objective of ACT is to increase psychological flexibility by fostering more meaning in one's life while modifying unhelpful relationships with internal and external experiences, thereby increasing access to a wider range of strategies for coping and recovery.[66] The six tenets of ACT are explored through a process-oriented approach that is less structured than other modalities. It differs from other cognitive approaches in its emphasis on symptom *management* and nonjudgmental present-moment awareness over symptom reduction and cognitive reappraisal.[66]

Similar to CBTp, acceptance and commitment therapy for psychosis (ACTp) has been modified for people with schizophrenia. Often cited as an emerging therapeutic approach for schizophrenia, ACTp has demonstrated effectiveness across settings and for individual and group formats.[63,66] ACTp has been shown to reduce distress related to positive symptoms and increase overall functioning.[66] Mindfulness-based frameworks included in ACTp and combined with other approaches have also been shown to specifically contribute to improvements in psychosis.[62,63,79]

COGNITIVE REMEDIATION TRAINING

Cognitive impairments are characteristic of schizophrenia and a central feature of the lower quality of life experienced in this population. Cognitive remediation training (CRT) is used to target the cognitive impairments associated with schizophrenia via computerized training and interactive games that strengthen and refine cognitive processes to improve functional capacity.[80,81] Critical components include detailed exercises, problem-solving, and real-world application.[68] CRT is related to improvements for negative symptoms as well as broader functional outcomes.[82] Social cognition paradigms may also be included, thereby improving interpersonal relationships and the underlying cognitive processes required. When included as part of another therapeutic approach or larger model, CRT adds significant therapeutic value toward recovery.[68,70]

METACOGNITIVE TRAINING AND THERAPIES

Similar to cognitive approaches, metacognitive trainings (MCTs) aim to understand and address cognitive biases and thinking patterns that may underlie and exacerbate symptoms of

psychosis. MCTs target these processes by increasing awareness and skills, while also considering how cognitions are related to relationships with oneself and the larger environment and focusing on the meaning and significance placed on cognitions.[83,84]

Modified MCTs such as metacognitive reflection and insight therapy (MERIT) and metacognitive training for psychosis have been specifically developed for people with schizophrenia. MERIT is an integrative MCT that incorporates narrative therapy and is informed by principles from third-wave mindfulness-based therapies. With a focus on "meaning-making" and crafting new narratives around cognitions and misattributions, MERIT aims to help shape the complex relationship that a person with schizophrenia has with themself and their experiences, leading to increased self-understanding and self-management, and influencing a more meaningful experience overall.[71,85] MCTs have been shown to improve positive symptoms, psychosocial functioning, metacognitive functions, and management of recovery.[71,72]

SOCIAL SKILLS TRAINING

Social skills training (SST) is designed to teach interpersonal skills to increase engagement and positive interactions. Isolation and social withdrawal are common consequences of schizophrenia.[86] SST addresses these challenges via effective communication, problem-solving, and social engagement, developed through strategies such as role-playing and coaching with feedback.[65,87] This approach aims to improve social connection and facilitate social support, which is a key prognostic indicator and critical factor for recovery. SST may be a focus of therapy or integrated with a broader approach such as CBTp, ACTp, or CRT. SST has been shown to increase engagement with peers and family members, increase confidence and effectiveness toward education and employment, and strengthen social engagement overall.[65,74]

EXPRESSIVE THERAPIES

Art, music, dance, and writing therapies have demonstrated effectiveness when added as adjunctive therapies. Expressive therapies allow individuals to connect with previously developed skill sets and hone new methods of exploring and understanding experiences. Review studies in people with schizophrenia have shown subjective improvements across symptom and functioning domains.[65,88] While expressive therapies may be more common in programmatic models (e.g., psychosocial rehabilitation), they are likely to be valuable when added to group sessions and individual therapy.

Table 1: Evidence-Based Individual Therapies for Psychosis

Therapy/Approach	Therapeutic Focus	Core Techniques
Cognitive behavioral therapy for psychosis	Cognitive restructuring for distorted beliefs and intrusive thoughts	• Symptom monitoring • Identification and development of alternative cognitions • Behavioral activation • Psychoeducation and relapse prevention
Recovery-oriented cognitive therapy	Cognitive restructuring informed by recovery, empowerment, hope, and purpose	• Activity scheduling • Strength-based engagement • Interpersonal connection
Acceptance and commitment therapy for psychosis and mindfulness-based therapies	Psychological flexibility and values-driven living	• Acceptance • Present-moment awareness • Values clarification and engagement • Process-oriented interventions
Cognitive remediation therapy	Cognitive enhancement and functional improvement	• Computerized exercises • Applied problem-solving • Social cognition paradigms
Metacognitive training/MERIT	Increased awareness of thinking processes and self-reflection	• Bias detection • Insight and awareness development • Narrative therapy approaches
Social skills training	Interpersonal effectiveness and social connection	• Role play and modeling • Communication skills • Problem-solving skills
Expressive therapies	Emotional expression, identity development, and creativity	• Use of skills in art, music, dance, and writing • Creative exploration and expression

Family therapy approaches

Family support has shown itself to be a potential positive influence on better outcomes for individuals living with schizophrenia.[89] When family members, caregivers, or other close support networks are present and engaged in care, individuals with schizophrenia are more likely to engage with treatment plans and progress toward recovery, which includes higher subjective quality of life, reduced relapse rates and hospitalizations, and less involvement with the legal

system.[90] Engaged families also promote environments with reduced stress and conflict, which can be a critical component for recovery.

Family psychoeducation programs are the most widely used family therapy approaches and include a variety of cognitive and therapeutic elements. They may be offered in individual or group formats and share the key components of collaboration, effective communication, problem-solving, and coping.[91,92] Other approaches such as the open dialogue model emphasize the importance of the larger network and facilitate a group meeting with an individual's support system and treatment team. The dialogic process offers a different set of skills and support aimed to increase shared understanding and compassion, while developing effective communication and reflective skills. This process has been incorporated into early intervention programs and treatment settings and has shown promising results for indicators such as reducing DUP and crisis management.[93] Family engagement in any modality is often a linchpin for recovery.

DIGITAL THERAPIES

Technological advances have broadened the methods for delivering mental health care for schizophrenia. While virtual reality programs have been used for some time for post-traumatic stress disorder and other trauma-related diagnoses, digital therapies for schizophrenia are relatively new. Newer approaches include AVATAR therapy, a virtual reality model designed for auditory hallucinations.[94,95] More smartphone-based apps are being designed to track experiences, manage symptoms, and provide support for a variety of symptom presentations.[96] The proliferation of smartphone applications is expected to continue to increase access to care, improve monitoring, and reduce DUP. At the same time, research is still required on these different applications as many get promulgated without clinical expertise or a research base to support them.[97]

PROGRAMMATIC MODELS OF CARE FOR PSYCHOSOCIAL INTERVENTION

Medication and psychotherapy are the frontline interventions for individuals living with schizophrenia. As previously discussed, there are several evidenced-based psychotherapy approaches and models that can be used, along with medication strategies, and integrated based on the needs of the individual. However, individuals living with and recovering from schizophrenia have a variety of psychosocial needs that may not be met by traditional clinical care. Complementary models of care include clubhouses and psychosocial rehabilitation programs. These environments address the social and community needs of individuals with schizophrenia by providing a physical space in which to engage with other individuals with a shared experience. Resources such as supported employment or job training, assistance with activities of daily living, and social activities and gatherings reflect collaboration between members and staff. These models have been shown to reduce isolation, increase overall functioning, and improve engagement with treatment teams all with an eye toward recovery.[98] Peer specialists are frequently leaders, offering critical representation that is significantly related to recovery rates in schizophrenia.[99] Psychosocial interventions aim to help individuals live full and meaningful lives with work, families, and other aspects of overall well-being. The more individuals are able to engage in work and family life, however, the more flexible the models will need to be for these supports. Single-session interventions, for example, may be useful to help

individuals access support while maintaining outside commitments.[100] It is imperative that multimodal therapeutic approaches continue to address the critical needs of individuals living with schizophrenia while keeping up with technological advances and reducing stigma. In the end, empathy, compassion, understanding, and investment in recovery will remain the bedrocks of effective care, in whatever shape it takes.

Pharmacotherapy

Medication can be an important part of a holistic treatment plan for people with schizophrenia. In this section, the medications used to treat schizophrenia and psychotic disorders and their mechanisms of action are reviewed. For state mental health leaders, service providers working with individuals with schizophrenia, families, payers, and others, this information is aimed to be informative given the many questions that arise in the context of care for people with psychotic disorders.

Note: This paper is for information purposes and does not constitute medical advice. Patients should consult their physicians about individual medical decisions.

In selecting an antipsychotic medication to treat a person with schizophrenia, not only must the individual's preference be honored, but psychiatric history and presentation, medical history, and potential drug–drug interactions must be considered. Even after a medication is agreed upon, people may not consistently take the antipsychotic as prescribed due to a myriad of factors, including side effects, lack of insight, illness-associated cognitive challenges, lack of trust in the system, psychotic symptoms, social pressures and stigmatization, and financial barriers.[106] Unanticipated issues pertaining to how medications interact with the person's physiology can also affect efficacy and contribute to side effects. Unexpected side effects, even if relatively minor, should always be addressed expediently to reduce the risk of such problems causing medication nonadherence. Involvement of family and other natural supports to help encourage adherence as well as monitor for both medication efficacy and side effects can be critical to successful treatment.

Whereas nonpharmacological interventions such as those discussed earlier play a critical role in supporting recovery and improving the quality of life of those with schizophrenia, those treatment modalities are most effective when integrated with appropriate pharmacological treatment. Antipsychotic medications remain the cornerstone of managing the core symptoms of schizophrenia. The APA and the British Association for Psychopharmacology guidelines recommend that individuals with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and adverse effects and that those who improve on an antipsychotic medication be continued on that treatment modality.[53,101]

Until late 2024, the only two classes of antipsychotic medications available for the treatment of schizophrenia were the first- and second- generation antipsychotic medications. These two medication classes have been the mainstay of pharmacotherapy treatment for the past 70 years and have focused on the dopamine-2 (D2) receptors.

While dopamine D2 receptor antagonists along with D2 receptor partial agonists (agonists and antagonists are terms used to describe how the medications are processed within the brain

within individual neurons) remain the mainstay in the pharmacological treatment for schizophrenia, their effectiveness varies across symptomatology.[102,103] They are most effective for core psychotic symptoms, such as delusions and hearing voices, and possibly minimally effective for negative and cognitive symptoms.[104,105] In addition to their effectiveness in acute treatment, antipsychotic medications significantly reduce the risk of relapse.[106,107,108,109] Whereas these medications, except for clozapine, have similar efficacy, they vary significantly in their adverse effect profiles.[110,111,112,113,114]

Dopamine D2 receptor antagonism is central to antipsychotic efficacy in treating schizophrenia spectrum disorders. However, many of these medications also bind to other receptors, influencing both clinical effects as well as side effects. Antipsychotic medications are traditionally grouped into one of two classes: first-generation, or typical, antipsychotics and second-generation, or atypical, antipsychotics. First-generation antipsychotics (FGAs) are held to be equally efficacious to each other, so treatment choice is largely based on predicted side effect profiles, clinical presentation and history, and patient preference. Although they are more frequently prescribed, FGAs are not less effective than second-generation antipsychotics (SGAs) as a class.[115,116] SGAs do seem to vary in efficacy and tolerability, likely due to diversity in mechanisms of action.[117,118] Choice of SGA should also be made in light of an individual's history and side effect risks as well as patient preference.

Dosing of medications plays an important role in effectiveness and safety. Early-course patients with schizophrenia often respond to antipsychotic medications that may not be as effective for people with multi-episode schizophrenia and also may respond at lower doses. Prescribing lowest effective doses of antipsychotics for all patients can minimize both acute and longer-term side effect risks. However, caution should be taken in ensuring doses are not too low. It is a difficult balance for the prescriber and patient to achieve this equilibrium. Continuous antipsychotic treatment at doses required for stabilization is generally recommended for multi-episode individuals. This strategy does not appear have an adverse effect on social functioning and also decreases the risk of psychiatric hospitalization.[119] Moreover, despite known side effects, long-term treatment with antipsychotics does not increase risk of hospitalization due to medical side effects, and they do decrease the risk of mortality.[120]

A new medication, xanomeline/trospium, was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia with an effect on the muscarinic receptor, which is different from the dopamine receptor, as described further below. Other innovations include routes of administration and duration of effectiveness that can be seen with long-acting formulations (see below). It is essential when considering which medication to select to consider not only the efficacy of the medication formulation but also the adverse effect profile, individual response, and importance of adherence.

A comprehensive, personalized treatment plan that incorporates both psychosocial and pharmacological strategies offers the best opportunity for symptom stabilization and sustained recovery. Several topics are discussed further in the following subsections: typical antipsychotics, atypical antipsychotics including clozapine, the muscarinic agonist, long-acting injectable antipsychotic formulations, and strategies for side effect monitoring.

TYPICAL ANTIPSYCHOTIC MEDICATIONS

Typical antipsychotics, or FGAs, are older antipsychotic medications that are categorized by how strongly they block the dopamine D2 receptor, which is described as "high," "medium," or "low potency." High-potency FGAs, like haloperidol and fluphenazine, bind to the D2 receptor and minimally bind to histaminic and muscarinic receptors. From PET studies, it has been suggested that when D2 receptor occupancy exceeds 60 to 80 percent,[121] binding will occur in the nigrostriatal pathway and precipitate extrapyramidal symptoms, or EPS, including drug-induced parkinsonism and dystonias. Binding in the tuberoinfundibular pathway leads to hyperprolactinemia and its associated side effects (e.g., galactorrhea, sexual dysfunction, and amenorrhea). Binding in the mesocortical pathway can precipitate "secondary negativism," which includes symptoms like amotivation and anhedonia. Low-potency FGAs, on the other hand, bind with relatively low affinity to the D2 receptor and high affinity to histaminic, alpha adrenergic, and muscarinic receptors. These medications, like chlorpromazine, are therefore less likely to cause EPS and hyperprolactinemia but are more likely to cause sedation, dry mouth, constipation, orthostatic hypotension, weight gain, and other side effects. Mid-potency FGAs have characteristics of both medication classes and are considered a sort of middle ground in terms of side effect profiles. Mid-potency FGAs include perphenazine and loxapine.

Dosing of FGAs is relative to potency. In other words, low-potency medications are prescribed at numerically high doses, mid-potency medication are prescribed at medium doses, and higher-potency medications are prescribed at low doses. Dosing is also frequently compared to equivalent doses of chlorpromazine. For example, 300 mg of low-potency chlorpromazine is generally considered equivalent to 10 mg of fluphenazine.[122]

ATYPICAL ANTIPSYCHOTIC MEDICATIONS

Clozapine (covered below) is largely considered to be the first atypical antipsychotic, or SGA. Subsequent SGAs were modeled after clozapine, with the goal of replicating its efficacy while minimizing some of its associated side effects. Importantly, none of the SGAs have been found to be as effective in the treatment of treatment-resistant schizophrenia as has clozapine, but SGAs remain an important class of medications. Like FGAs, all target dopamine D2 receptors, but like clozapine, they also incorporate high-affinity, serotonergic 5-HT2A binding and antagonism. It is this mechanism of action that sometimes leads to this class of medications being called serotonin-dopamine antagonists, or SDAs. In theory, binding 5-HT2A receptors leads to reduced risk of EPS.[123] Also, like clozapine, most of these medications do not bind as potently or as tightly at the D2 receptor and dissociate more quickly, which may independently decrease EPS risk.[105] 5-HT2A binding may also have some procognitive effects,[107] supporting theories that SGAs would positively affect negative and cognitive symptoms of schizophrenia. Unfortunately, evidence for substantial improvement in those symptom domains with either FGAs or SGAs remains limited.

As drug discovery has progressed, therapeutic benefit associated with antagonism at additional receptors has also been explored, as has utilizing partial or full agonism at different receptors. Aripiprazole was first in its class of partial dopamine receptor agonists, followed by brexpiprazole and cariprazine. Lumaterperone is a partial agonist at presynaptic D2 receptors.

CLOZAPINE

First synthesized in 1958, clozapine was initially FDA approved in 1989. It is currently FDA approved for (1) treatment-resistant schizophrenia and (2) reducing suicidal behavior in persons with schizophrenia or schizoaffective disorder. The *American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia* also suggests clozapine if the risk for aggressive behavior remains substantial despite other treatments.[53]

Treatment-resistant schizophrenia causes considerable suffering and an estimated $34 billion in direct medical costs to the United States; individuals have high rates of suicidal ideation, smoking, and substance abuse.[124] A meta-analysis of 21 studies found clozapine to have superior efficacy for treatment-resistant schizophrenia for positive symptoms in the short and long terms. Despite its unparalleled efficacy, it remains highly underutilized in the United States in comparison with other countries, with around 5 percent of people with schizophrenia taking clozapine.[125] Unfortunately, clozapine use has remained relatively static across the United States from 2016 to 2023, with approximately 147,000 patients prescribed clozapine in 2023.[126]

Clozapine's risk of severe neutropenia (decrease in the types of white blood cells used to fight infections) and the need for hematologic monitoring are commonly reported as a key barrier to its wider use.[127] Severe neutropenia, defined by an absolute neutrophil count (ANC) of less than 0.5, occurs in about 0.9 percent of people exposed to clozapine, and is most likely to occur early after its initiation.[128] In February 2025, the FDA eliminated the reporting requirements of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) protocol, potentially reducing the administrative burden on prescribers, pharmacies, and patients. Although the change may increase clozapine use, many barriers remain and the impact of the change is yet to be determined.

Clozapine has important benefits in reducing suicidal behavior and risk of violence. The lifetime risk of suicide in patients with schizophrenia is 4.9 percent.[129] In the InterSePT study, clozapine was associated with less suicidal behavior and suicide attempts compared with olanzapine.[130] In a study combining Swedish and Finnish registry data, clozapine was the only antipsychotic associated with a decreased risk of suicide.[131] When compared with olanzapine and haloperidol, clozapine was more effective in reducing physical assaults.[132]

> "Before clozapine, I was lost in psychosis. I spent years locked in my room—not speaking, not showering, barely eating. I had lost the ability to read or even hold a conversation. I was completely disconnected from reality. After 13 failed antipsychotics, my doctors said I was gravely disabled and would likely need to live in an institution. Then I was given clozapine—it saved my life and gave me my mind back. Now I drive, I have friends, a girlfriend, a college degree, and plans to earn my master's in social work. Clozapine didn't just improve my symptoms—it gave me a future. Everyone with schizophrenia deserves that same chance."
>
> —Michael Brisbin, person taking clozapine and clozapine advocate

IDENTIFYING CLOZAPINE CANDIDATES

Any prescriber who treats patients with schizophrenia should have a working knowledge of clozapine or at least should be able to appropriately identify candidates for this medication. Rather than viewed as a "last resort," clozapine should be considered after failure of two antipsychotic medications of an adequate dose and duration. It is estimated that about one-quarter of people with schizophrenia have an element of treatment resistance during the first episode,[133] with others developing treatment resistance over time. Discussing clozapine should not be seen as a one-time conversation, but rather as an ongoing dialogue.

When evaluating patients, it is essential to identify treatment-resistant schizophrenia as early in the illness as possible, since delays in the time to initiate therapy with clozapine can lead to a decreased response. One study found that when the delay to clozapine initiation after the diagnosis of treatment-resistant schizophrenia was less than 2.8 years, the response was 81.6 percent, but if the delay was greater than 2.8 years, the response decreased to 30.8 percent.[134] Further contributing to the importance of early initiation, a Finnish cohort study found that for first-episode individuals with schizophrenia, switching to clozapine after the first relapse significantly reduced the risk of a second relapse, but continuing the same antipsychotic or switching to a different non-clozapine antipsychotic offered no benefit.[135]

Treatment-resistant schizophrenia can be difficult to untangle from a lack of adherence to pharmacotherapy for the treatment of schizophrenia. Signs to consider as predictors of treatment-resistant schizophrenia include positive symptoms (e.g., ongoing hallucinations or delusions) on long-acting injectable antipsychotics (LAIs), sensitivity to EPS from conventional D2 blockers, young age of onset, and occurrence of treatment-resistant schizophrenia immediately after the onset of symptoms. It can also occur over time.[136]

Several clues may help prescribers identify clozapine candidates, which may include individuals taking two or more antipsychotics, persistent positive symptoms for those on LAIs, or significant susceptibility to drug-induced movement disorder side effects from dopamine receptor blockers. Moving forward, health systems should consider using informatics and decision support to help prescribers identify clozapine candidates.

INITIATING CLOZAPINE

Although dosing recommendations vary significantly across published titration schedules for clozapine, slower titration may improve tolerability and safety.[137] The U.S. package insert does not take into account several variables, including smoking status, patient heritage, site of treatment, and presence of CYP inhibitors or inducers. Clinicians should consider all of these variables in titration to maximize individual acceptance and to minimize safety issues.[138] Additionally, a documented plan for the cross-taper with other antipsychotic(s) should be developed.

Clozapine is generally dosed at bedtime (rather than divided dosing) in North America without loss of efficacy.[139] There is not one single recommended titration strategy, and titration is based on individual factors such as clinical urgency, setting (inpatient/outpatient), concurrent medication, patient's ancestral heritage (e.g., individuals of Asian ancestry may need slower titration), and response/tolerability to early doses. Slow titrations may be better tolerated and are less associated with fever and clozapine-induced myocarditis.[140]

The dosage of clozapine is titrated gradually to minimize adverse effects. Titration typically starts at 12.5 mg nightly. The total daily dose is then increased by increments of 25 or 50 mg per day, every 2 or 3 days, as tolerated by the individual. An example of an inpatient titration would be a total daily dose of 100 mg per day at the end of week one, and 200 mg per day at the end of week two. Titration can then continue at a similar rate to between 300 and 450 mg per day, until efficacy becomes apparent. Plasma clozapine levels can be utilized when there may be unexpected adverse effects or lack of efficacy.[141] Dosing should be based primarily on the patient's clinical status and tolerability, rather than the level alone. The maximum dosage of clozapine in the United States is 900 mg per day.[125] The titration schedule should be customized for older adults or patients who are sensitive to adverse effects.

When starting clozapine, if the person is taking another antipsychotic medication and they are tolerating it, the medication should be continued until the clozapine begins to be effective. For oral antipsychotic medications, the clinician can start to taper the existing antipsychotic medication when the clozapine dosage is between 100 mg and 200 mg per day. A typical approach is to reduce the dose by 25 percent per week. Close monitoring of psychotic symptoms and antipsychotic adverse effects should occur, and the speed of the taper should be adjusted. If the person has been on a LAI antipsychotic medication, the dose can be lowered or discontinued, depending on the response to clozapine. If needed for further symptom control, oral antipsychotics can be used during the transition to clozapine.

If an individual has missed more than 2 days of medication, the dose should be substantially reduced. The clinician should consider the duration of not taking the medication and the potential risks and benefits, with consideration of restarting at 12.5 mg once or twice a day.[125] Then, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment. If discontinuing clozapine for a non-urgent reason, reduce the dose gradually over a period of 1 to 2 weeks or more. Monitoring should occur more closely, as there is a risk of exacerbation of psychosis from lowering of clozapine dosage.[142]

CLOZAPINE DRUG–DRUG INTERACTIONS

According to the manufacturer's package insert, clozapine concentrations may be increased by specific enzyme inhibitors and decreased by inducers.[125] The polycyclic aromatic hydrocarbons in cigarette smoke (not the nicotine) cause clozapine to be broken down more rapidly.[143] Individuals who smoke cigarettes may need up to a twofold increase in dose, whereas a 30 to 40 percent reduction in dose may be necessary if an individual discontinues or is unable to smoke.[144] Additionally, smoking cannabis several times daily may also increase clozapine's metabolism.[145] Caution should be used when co-administered with particular enzyme inhibitors.[125] In addition to these interactions, caution should be used with the use of other medications that are myelosuppressive, anticholinergic, or hypotensive, or have sedative properties. Benzodiazepines in combination with clozapine may cause respiratory depression and hypotension, so caution is advised when co-prescribing.[146]

CLINICAL MONITORING OF EFFICACY

Patients taking clozapine should be monitored for treatment effectiveness at each clinical visit. In the acute stabilization phase, in addition to a decrease in symptomatology, a reduction in self-harm and harm to others should be noted. Psychotic symptom response should be evaluated by direct observation and/or interview with the patient regarding the quality of hallucinations and

delusions and the level of disorganized thinking. During the stabilization and maintenance phase, there should be a continued decrease in positive, negative, and cognitive symptoms. Improvement in psychosocial functioning, social deficits, and activities of daily living will also improve during this time. Additionally, the individual should be routinely monitored for adverse effects, adherence, and worsening or recurrence of symptoms.[53]

CLOZAPINE ADVERSE EFFECTS

Numerous adverse effects are associated with clozapine, including drooling, sedation, weight gain, constipation, dizziness, metabolic symptoms, severe neutropenia, and hypotension.[152] **Table 2** describes the treatment recommendations for several of these potential adverse effects.

In addition to the standard antipsychotic medication monitoring, and as noted above, clozapine requires ANC monitoring due to the risk of agranulocytosis per the package labeling. As of February 24, 2025, the FDA announced that it does not expect prescribers, pharmacies, and individuals in care to participate in the REMS program for clozapine or to report results of an ANC blood test before pharmacies dispense clozapine.[148]

The greatest risk of severe neutropenia is during the first 18 weeks after clozapine's initiation.[149] The prescribing information for clozapine requires monitoring the ANC weekly for the first 6 months, then every other week for months 6 through 12, then monthly thereafter, indefinitely.[125] Severe neutropenia can be life threatening, but clozapine has other important adverse effects such as ileus (meaning paralysis for the intestine) and pneumonia, which also are associated with mortality.[150] See clozapine ANC monitoring and treatment recommendations in **Table 3.**

Benign ethnic neutropenia (BEN) is a condition observed in certain ethnic groups including those of African descent and several Jewish, Middle Eastern, and Afro-Caribbean groups, whose average ANCs are lower than standard laboratory ranges for neutrophils.[151] Patients with BEN are not at increased risk of developing clozapine-induced neutropenia.[152] There is no definitive diagnostic test for BEN, and diagnosis is made on clinical judgment. Additionally, there is no increased risk of infections in this group.[153] Individuals with BEN do have a different ANC algorithm for clozapine management due to their lower baseline ANC levels.

In addition to ANC monitoring, individuals starting on clozapine should have their vital signs, including blood pressure, pulse, temperature, and weight, monitored daily for the first 2 weeks and then weekly through week 8. Weekly serum creatinine should be monitored to screen for interstitial nephritis (related to kidney function) for the first 8 weeks.[126] In addition, for the first 4 to 8 weeks, troponin I/T and C-reactive protein should be obtained weekly for myocarditis screening.[154] Please see **Figure 4** for more details.

Table 2: Adverse Effects and Treatment Recommendations Associated with Clozapine

Adverse Effects	Treatment Recommendations
Cardiometabolic symptoms	• Taper/discontinue other contributors • Encourage physical activity, lifestyle programs, and diet modification. • Consider prophylactic metformin for high-risk agents[1] • Glucagon-like peptide-1 and gastric inhibitory polypeptide receptor agonists[2]
Constipation	• Prevention: Reduce opioids, iron, and anticholinergics; encourage activity; hydration; avoid bulk laxatives[3] • Bowel regimen[3,4] • Prophylactic docusate 250 mg oral PO twice daily with rescue as needed (magnesium citrate 150 mL or magnesium hydroxide 30 mL PO every 2 days without bowel movement) • Add one osmotic laxative if docusate is ineffective (polyethylene glycol 17 g oral PO every morning) • Add one stimulant laxative if osmotic laxative is ineffective (sennosides 17.2 mg or bisacodyl starting at 5 mg PO every night at bedtime) • Add secretagogue with consideration of tapering other agents (linaclotide, lubiprostone)
Myocarditis	• Discontinue clozapine and obtain cardiac evaluation (EKG, TTE, ECG, transthoracic echocardiogram, cardiac MRI)[5] • Clozapine rechallenges have been successful[6]

Sialorrhea	• Atropine 1% ophthalmic solution 1–2 drops sublingual every 2–4 hours as needed • Ipratropium bromide 0.06% nasal spray 1–2 puffs under the tongue every 4–6 hours as needed[3]

[1] Carolan A, Hynes-Ryan C, Agarwal SM, et al. Metformin for the prevention of antipsychotic-induced weight gain: guideline development and consensus validation. Schizophr Bull. Published online December 9, 2024:sbae205. doi:10.1093/schbul/sbae205

[2]Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038

[3] Meyer JM, Stahl SM. The Clozapine Handbook. Cambridge University Press; 2019. doi:10.1017/9781108553575

[4] Every-Palmer S, Ellis PM, Nowitz M, et al. The Porirua Protocol in the treatment of clozapine-induced gastrointestinal hypomotility and constipation: a pre- and post-treatment study. CNS Drugs. 2017;31(1):75-85. doi:10.1007/s40263-016-0391-y

[5] Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust N Z J Psychiatry. 2011;45(6):458-465. doi:10.3109/00048674.2011.572852

[6] Cook SC, Ferguson BA, Cotes RO, Heinrich TW, Schwartz AC. Clozapine-induced myocarditis: prevention and considerations in rechallenge. Psychosomatics. 2015;56(6):685-690. doi:10.1016/j.psym.2015.07.002

PO = per os (by mouth).

Table 3: Clozapine ANC Monitoring and Treatment Recommendations

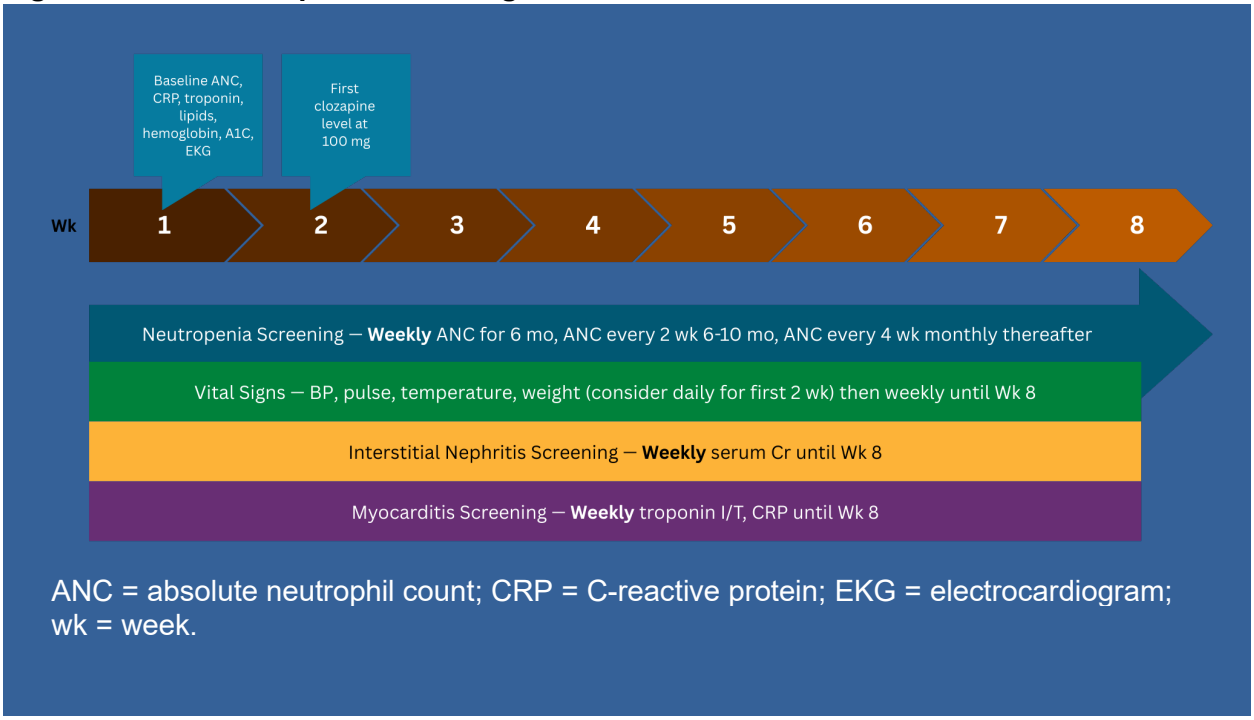
ANC Level	Treatment Recommendations	ANC Monitoring Requirements for General Population
Normal range (≥ 1500 mcL)	• Initiate treatment with clozapine • If treatment interrupted: • < 30 days: Continue monitoring as before • ≥ 30 days: Monitor as if new patient	• Weekly from initiation to 6 months, then every 2 weeks from 6 to 12 months, then monthly after 12 months
Mild neutropenia (1000–1499 mcL)	• Continue treatment	• Three times weekly until ANC ≥ 1500 mcL • Once ANC ≥ 1500 mcL, return to patient's last "normal range" ANC monitoring interval

Moderate neutropenia (500–999 mcL)	• Recommend a hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC ≥ 1000 mcL	• Daily until ANC ≥ 1000 mcL, then three times weekly until ANC ≥ 1500 mcL • Once ANC ≥ 1500 mcL, check ANC weekly for 4 weeks, then return to patient's last "normal range" ANC monitoring interval
Severe neutropenia (< 500 mcL)	• Recommend a hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless the prescriber determines benefits outweigh risks	• Daily until ANC ≥ 1000 mcL, then three times weekly until ANC ≥ 1500 mcL • If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥ 1500 mcL
Normal BEN range (established ANC baseline ≥ 1000 mcL)	• Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted: • < 30 days: Continue monitoring as before • ≥ 30 days: Monitor as if new patient	• Weekly from initiation to 6 months, then every 2 weeks from 6 to 12 months, then monthly after 12 months
BEN neutropenia (500–999 mcL)	• Recommend a hematology consultation • Continue treatment	• Three times weekly until ANC ≥ 1000 mcL or at patient's known baseline • Once ANC ≥ 1000 mcL or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "normal BEN range" ANC monitoring interval
BEN severe neutropenia (< 500 mcL)	• Recommend a hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless the prescriber determines benefits outweigh risks	• Daily until ANC ≥ 500 mcL, then three times weekly until ANC at patient's baseline • If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥ 1000 mcL or at patient's baseline

Information from manufacturer's package inserts.

Abbreviations: ANC = absolute neutrophil count; BEN = benign ethnic neutropenia.

Figure 4: Initial Clozapine Monitoring



—Adapted from Correll CU, Agid O, Crespo-Facorro B, et al. A guideline and checklist for initiating and managing clozapine treatment in patients with treatment-resistant schizophrenia. CNS Drugs. *2022;36(7):659-679. doi:10.1007/s40263-022-00932-2*

Beyond the monitoring described for all antipsychotics and blood monitoring, patients taking clozapine should be monitored for the management of constipation and gastrointestinal hypomotility. The FDA strengthened its warning in 2020, stating that constipation caused by clozapine can progress to serious bowel complications that can lead to hospitalization or even death if not diagnosed and treated quickly.[155] Patients should be asked about their bowel function at least weekly when starting clozapine, and a prophylactic bowel regimen should be started upon initiation of clozapine. The Bristol stool chart can assist in determining stool morphology.[156]

MUSCARINIC AGONISTS

In the fall of 2024, the FDA approved xanomeline/trospium for the treatment of schizophrenia. This medication has the first new mechanism for the treatment of schizophrenia in more than 70 years. Xanomeline was initially developed to treat the symptoms of Alzheimer's disease, and during those research studies it was shown that the drug demonstrated antipsychotic-like properties in rodents.[157] These findings led to an initial 4-week trial, in which xanomeline improved scores on the total Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale, as well as measures of verbal learning and short-term memory function.[158] However, the gastrointestinal effects limited the movement of xanomeline into clinical practice.

In subsequent years, a coformulation of xanomeline and trospium was developed, with trospium added as a muscarinic receptor antagonist with minimal, if any, penetration of the blood–brain

barrier. The mechanism of trospium would block the unwanted peripheral adverse effects of xanomeline.[159]

Xanomeline binds to muscarinic receptors M1 to M5 with comparable affinity, although it exhibits higher agonist activity at the M and M4 receptors. The M1 and M4 receptor activation in the central nervous system may lead to the reduction of presynaptic dopamine release in striatal regions. Trospium is an antagonist of muscarinic receptors outside of the central nervous system that is believed to improve the tolerability of xanomeline when the two are used in combination.[160,161] Together, these medications provide upstream impact on downstream dopamine and a mechanism to avoid peripheral gastrointestinal difficulties. Please see **Table 4** for a summary of the results of the clinical trials to date regarding xanomeline/trospium.

XANOMELINE/TROSPIUM CLINICAL USE

According to the manufacturer's package insert, xanomeline/trospium dosing should be initiated at 50/20 mg orally twice daily for at least 5 days and then increased if necessary to 125/30 mg orally twice daily.

Based on pivotal trials, xanomeline/trospium is contraindicated in those with gastric retention, moderate or severe hepatic impairment, untreated narrow-angle glaucoma, and urinary retention. The most frequently reported adverse effects identified in the studies were nausea, dyspepsia, constipation, vomiting, and hypertension. Additional concerning adverse effects include urinary retention, increased heart rate, and reduced gastrointestinal movement. The medication carries a risk of liver damage, and patients with moderate to severe renal or hepatic impairment are advised against its use.[148]

Based on package labeling, strong CYP2D6 inhibitors may increase xanomeline concentrations, while medications that are eliminated by active tubular secretion may increase trospium concentrations when these medications are concomitantly used together.[162] The medication inhibits CYP3A4 and P-glycoprotein locally in the gastrointestinal tract. Additionally, caution is warranted when using xanomeline/trospium concomitantly with other antimuscarinic medications. Interactions with other antipsychotic medications should be monitored because current data is lacking in potential additive effects of anticholinergic effects.[148]

XANOMELINE/TROSPIUM MONITORING PARAMETERS, LIMITATIONS, AND PLACE IN CLINICAL PRACTICE

The monitoring recommendations for xanomeline/trospium are similar in nature to those for the first- and second-generation antipsychotics. Heart rate, liver enzymes, bilirubin, and blood pressure should be assessed at baseline and periodically as indicated.

There are several limitations to consider with xanomeline/trospium including the twice-daily dosing on an empty stomach. If the medication is taken with food, the bioavailability of trospium is decreased, potentially increasing the gastrointestinal adverse effects of xanomeline. In addition to the dosing and adverse effects, the cost of the branded product and lack of clinical guidance on utilization may limit the use of the medication.

Clinical guidelines have not yet incorporated recommendations or placement in therapy for xanomeline/trospium. Currently, there is a paucity of data available on the comparison of xanomeline/trospium to other antipsychotic medications.

Table 4: Clinical Trials with Xanomeline/Trospium

Trial	Design	Intervention	Inclusion/Exclusion Criteria	Results
EMERGENT-1 (NCT03697252)[1]	Inpatient, phase 2, 5-week, double-blind, placebo-controlled, randomized controlled trial	• XT 50 mg/20 mg twice daily, then increased to 125 mg/30 mg twice daily; option to decrease to 100 mg/20 mg twice daily if adverse effects were unmanageable (*n* = 90) • Placebo (*n* = 92)	• Inclusion:18–60 years old; diagnosis of schizophrenia by DSM-5 and CGI-S score of ≥ 4, PANSS ≥ 80 with a score of > 5 on one positive symptom item or > 4 on two positive symptom items; experiencing an acute psychotic exacerbation or relapse of psychosis requiring hospitalization • Exclusion: History of treatment resistance to two adequate courses of antipsychotic medications and/or decrease in the PANSS total score by more than 20% between screening and baseline assessment	• Greater decrease in PANSS total score at week 5 with XT vs. placebo (−17.4 vs −5.9, $p < 0.001$) (Cohen's *d* 0.75) • Overall discontinuation rates (20% vs 21%) • Most common TEAEs constipation (17%), nausea (17%), dry mouth (9%), dyspepsia (9%), and vomiting (9%)

EMERGENT-2 (NCT04659161)[2]	Inpatient, phase 3, five-week, double-blind, randomized controlled trial	• XT 50 mg/20 mg for two days, then 100 mg/20 mg, then on day 8 125 mg/30 mg as tolerated (*n* = 126) • Placebo (*n* = 126)	• Inclusion:18–65 years old; diagnosis of schizophrenia by DSM-5; acute exacerbation or relapses of psychotic symptoms requiring hospital admission with onset < 2 months before screening • PANSS total score 80–120 with a score of ≥ 4 on at least two symptoms (delusions, disorganization, hallucinations, and suspiciousness or persecution) • CGI-S score of ≥ 4 • Exclusion: Primary disorders other than schizophrenia within the last 12 months; history of treatment resistance to antipsychotic medications; decrease in PANSS total score of 20% or more between screening and baseline	• Greater decrease in PANSS total score at week 5 with XT vs. placebo (−21.2 vs −11.6, $p < 0.0001$) (Cohen's *d* 0.61) • Overall discontinuation rates were similar between XT and placebo (25% vs. 21%) • Most common TEAEs were constipation, dyspepsia, nausea/vomiting, hypertension, dizziness, and GERD

EMERGENT-3 (NCT04738123)[3]	Inpatient, phase 3, 5-week, double-blind, randomized controlled trial	• XT 50 mg/20 mg for two days, then 100 mg/20 mg, then on day 8 125 mg/30 mg as tolerated (*n* = 125) • Placebo (*n* = 131)	• Inclusion/exclusion criteria the same as EMERGENT-2 trial	• Greater decrease in PANSS total score at week 5 with XT vs. placebo (−20.6 vs. −12.2, p < 0.001) (Cohen's *d* 0.60) • Overall discontinuation rates were similar between XT and placebo (36.8% vs. 29%) • Most common TEAEs were nausea/vomiting, dyspepsia, constipation, hypertension, and diarrhea

[1] *Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia.* N Engl J Med. *2021;384(8):717-726. doi:10.1056/NEJMoa2017015*

[2] *Kaul I, Sawchak S, Correll CU, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial.* Lancet. *2024;403(10422):160-170. doi:10.1016/S0140-6736(23)02190-6*

[3] *Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial.* JAMA Psychiatry. *2024;81(8):749-756. doi:10.1001/jamapsychiatry.2024.0785*

Abbreviations: CGI-S = Clinical Global Impression Severity Scale; DSM = Diagnostic and Statistical Manual; *EPS = extrapyramidal symptoms; GERD = gastroesophageal reflux disease; PANSS = Positive and Negative Syndrome Scale; TEAEs = treatment-emergent adverse effects; XT = xanomeline-trospium.*

LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Medication adherence can be poor across both physical and psychiatric disorders.[163] It is particularly poor in persistent disorders where treatments are designed to prevent symptom onset or recurrence and the consequences of stopping treatment are delayed. Approximately 75 percent of individuals with schizophrenia become nonadherent to treatment within 2 years of hospital discharge.[164]

When originally developed, second-generation antipsychotic medications were thought to be at least as efficacious as the first-generation medications but were less likely to cause EPS. With the decreased risk of these adverse effects, it was believed that adherence to treatment would improve. Unfortunately, this was not true.[165] Individuals receiving SGAs still have high rates of nonadherence when reviewing 12-month adherent fill rates.[166]

There are many potential advantages to the use of long-acting injectable antipsychotics (LAIs) in the treatment of schizophrenia. These include the reduction in dosage deviations over the course of treatment, the elimination of questionable adherence status and need for the patient to take a daily medication, the establishment of the date of nonadherence should an injection be missed, the disentanglement for rationale of poor response to medication, establishment of a relationship between the dose and therapeutic drug monitoring, predicted plasma levels, and potential elimination of abrupt loss of efficacy if an injection is missed.[167,168,169,170]

Beyond those advantages, four unique benefits of LAIs have been established in clinical practice and literature: (1) decreasing hospitalization, (2) preventing relapse, (3) improving adherence, and (4) decreasing mortality. Compared with their oral formulation, LAIs have demonstrated lower risks of rehospitalization after the first hospitalization for schizophrenia.[171] In a systematic review and comparative meta-analysis, including 137 studies comparing LAIs with oral antipsychotic medications, LAIs were associated with a lower risk of hospitalization or relapse compared with the oral antipsychotic medications in randomized controlled trials, cohort studies, and pre–post studies.[172] Medicaid claims data from the Truven Health Analytics MarketScan database from multiple U.S. states demonstrated that adults discharged to community following index hospitalization initiated on an LAI had an adjusted odds ratio of being nonadherent lower compared with oral antipsychotic medication treatment.[173] An all-cause mortality study in Sweden of all patients ages 16 to 64 with schizophrenia diagnosis (*N* = 29,823) with a 7.5 year follow-up had the lowest mortality rate for second-generation LAIs. In pairwise comparisons LAIs were associated with 33 percent lower mortality than equivalent orals (0.67; 0.56, 0.80).[174] In a 10-year follow-up study, early relapses after the first episode (< 3 years) in patients had the poorest long-term outcomes including higher suicide attempts, violence episodes, more hospitalization, and lower employment. Delaying the first relapse may help to improve long-term outcomes.[175]

LAIs are unique formulations designed to improve patient outcomes by extending dosing intervals. Before a prescriber initiates an LAI, the patient must first demonstrate tolerability with the oral dosage formulation of the medication. **Table 5** provides details on the currently available LAIs.

Table 5: Long-Acting Injectable Antipsychotic Medications, First-Generation Antipsychotics

Medication	Route of Administration and Site of Administration	PO Overlap	PO Equivalents	Dosing Intervals	Clinical Pearls[a]

Haloperidol decanoate (Haldol)	• Intramuscular • Deltoid or gluteal	Continue PO dose for the first 2–3 injections if not using loading dose	• Initial loading dose = 20 times total oral daily dose • Maintenance dose = 10–15 times total PO daily dose	4 weeks	• Sesame seed–based oil • Z-track administration
Fluphenazine decanoate (Prolixin)	• Intramuscular; Subcutaneous • Deltoid or gluteal	Continue oral, decrease PO dose by 50% after 1st injection, discontinue PO after 2nd injection	10 mg oral = 12.5 mg LAI	2–4 weeks	• Sesame seed–based oil • Z-track administration

Long-Acting Injectable Antipsychotic Medications, Second-Generation Antipsychotics, Risperidone Products

Medication	Route of Administration and Site of Administration	PO Overlap	PO Equivalents	Dosing Intervals	Clinical Pearls[a]
Risperidone microspheres (Risperdal Consta)	• Intramuscular • Deltoid or gluteal	21 consecutive days	• 1 mg PO = 12.5 mg LAI • 2–3 mg PO = 25 mg LAI • 3–5 mg PO = 37.5 mg LAI • 4–5 mg PO = 50 mg LAI	2 weeks	• Refrigeration required • Must be administered within 6 hours of mixing

Risperidone (Perseris); July 2024: Discontinuation of sales and marketing; May 2025: Last product manufactured with expiration date of October 2026	• Subcutaneous • Abdomen or back of the upper arm	Not required	• 3 mg PO = 90 mg LAI • 4 mg PO = 120 mg LAI	4 weeks	Requires 60 cycles of mixing between syringes
Risperidone (Uzedy)	• Subcutaneous • Abdomen or back of the upper arm	Not required	• 2 mg PO = 50 mg LAI every 4 weeks or 100 mg LAI every 8 weeks • 3 mg PO = 75 mg LAI every 4 weeks or 150 mg LAI every 8 weeks • 4 mg PO = 100 mg LAI every 4 weeks or 200 mg LAI every 8 weeks • 5 mg PO = 125 mg LAI every 4 weeks or 250 mg LAI every 8 weeks	4 weeks or 8 weeks	Requires whipping of syringe to move air bubble to top of syringe before administration

Long-Acting Injectable Antipsychotic Medications, Second-Generation Antipsychotics, Olanzapine

Medication	Route of Administration and Site of Administration	PO Overlap	PO Equivalents	Dosing Intervals	Clinical Pearls[a]
Olanzapine pamoate (Zyprexa Relprevv)	• Intramuscular • Gluteal	Not required	• Initial 8 weeks: 10 mg PO = 210 mg LAI every 2 weeks or 405 mg LAI every 4 weeks • 15 mg PO = 300 mg LAI every 2 weeks • 20 mg PO = 300 mg LAI every 2 weeks • Maintenance dose: • 10 mg PO = 150 LAI every 2 weeks or 300 mg LAI every 4 weeks • 15 mg PO = 210 mg LAI every 2 weeks or 405 mg LAI every 4 weeks • 20 mg PO = 300 mg LAI every 2 weeks	2–4 weeks	REMS requires 3-hour post-injection monitoring for PDSS

Long-Acting Injectable Antipsychotic Medications, Second-Generation Antipsychotics, Paliperidone Products

Medication	Route of Administration and Site of Administration	PO Overlap	PO Equivalents	Dosing Intervals	Clinical Pearls[a]

Paliperidone palmitate (Invega Sustenna)	• Intramuscular • Loading dose: deltoid Maintenance dose: deltoid or gluteal	Not required	• Initiation dose: 234 mg LAI day 1, followed by 156 mg LAI day 8, followed by maintenance dose 5 weeks after 1st injection • (second initiation dose can be given within +/− 4 flexible window) • Maintenance dose: • 3 mg PO = 39–78 mg LAI • 6 mg PO = 117 mg LAI • 9 mg PO = 156 mg LAI • 12 mg PO = 234 mg LAI	4 weeks	• Requires sustained shaking before administration • Requires two injections as a loading dose
Paliperidone palmitate (Invega Trinza); Stabilization with Sustenna required before initiation	• Intramuscular • Deltoid or gluteal	Not required	• Invega Sustenna dose: • 39 mg = N/A • 78 mg = 273 mg Trinza • 117 mg= 410 mg Trinza • 156 mg= 546 mg Trinza • 234 mg= 819 mg Trinza	12 weeks	Requires sustained shaking before administration

Paliperidone palmitate (Invega Hafyera); Stabilization with Sustenna or Trinza required before initiation	• Intramuscular • Gluteal	Not required	• 1092 mg Hafyera = 156 mg Sustenna or 546 mg Trinza • 1560 mg Hafyera= 234 mg Sustenna or 819 mg Trinza	24 weeks	Requires sustained shaking before administration
Paliperidone palmitate (Erzofri); Not available for purchase in U.S. at time of publication	• Intramuscular • Initial dose: Deltoid Monthly doses: Deltoid or gluteal	Not required	• Initial dose: 351 mg • Not provided in package insert, but thought to be similar to paliperidone palmitate monthly per expert opinion	4 weeks	

Long-Acting Injectable Antipsychotic Medications, Second-Generation Antipsychotics, Aripiprazole Products

Medication	Route of Administration and Site of Administration	PO Overlap	PO Equivalents	Dosing Intervals	Clinical Pearls[a]
Aripiprazole monohydrate (Abilify Maintena)	• Intramuscular • Deltoid or gluteal	14 consecutive days if not using the 1-day initiation	• 15 mg PO = 300 mg LAI • 20 mg PO = 400 mg LAI	4 weeks	Prefilled syringes and vials available
Aripiprazole monohydrate (Abilify Asimtufii)	• Intramuscular • Gluteal	14 consecutive days if not currently receiving Abilify Maintena or using the 1-day initiation	• 10 mg PO = 960 mg LAI • 20 mg PO= 960 mg LAI	8 weeks	Can convert from PO aripiprazole or Abilify Maintena
Aripiprazole lauroxil (Aristada)	• Intramuscular • 441 mg: Deltoid • 662 mg, 882 mg, or 1064 mg: • Gluteal	21 consecutive days if Aristada Initio is not used	• 10 mg PO = 441 mg LAI every 4 weeks • 15 mg PO = 662 mg LAI every 4 weeks, 882 mg LAI every 6 weeks, 1064 mg LAI every 8 weeks • 20 mg PO = 882 mg IM every 4 weeks	4, 6, or 8 weeks	• Medication syringe should be tapped on hand, and then vigorously shaken • Medication must be rapidly administered
Aripiprazole lauroxil nanocrystal (Aristada Initio)	• Intramuscular • Deltoid or gluteal	N/A	675 mg given as a one-time dose with Aristada to avoid the necessary PO overlap Aristada	N/A	For the initiation of Aristada when used for the treatment of schizophrenia

According to manufacturer's package inserts.

IM = intramuscular; LAI = long-acting injectable antipsychotics; PDSS = post-injection delirium/sedation syndrome; PO = oral; REMS = risk evaluation and mitigation strategies.

[a] Refer to package insert for complete details on preparation and administration of the medication formulation.

ADVERSE EFFECTS OF LAI ANTIPSYCHOTIC MEDICATIONS

Adverse effects from LAIs are similar in nature and incidence to their oral counterparts, including hyperprolactinemia, extrapyramidal movement disorders, anticholinergic effects, sedation, QTc interval prolongation, and metabolic syndromes.[176] A systematic review of nonsystematic adverse effects of LAIs found that injection site pain was the most reported adverse effect, although there was a low incidence of injection site adverse effects associated with LAI antipsychotics. Additionally, each LAI is of varying injection volume, which can also contribute to injection site pain, with some injections upwards of 4–5 mL per injection. Overall, the LAIs are well tolerated by the patients receiving them.[177]

FORMULARY CONSIDERATIONS/PLACE IN CLINICAL PRACTICE

Current treatment guidelines from the APA recommend that patients receive treatment with an LAI antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence with oral medications.[53] Consideration should be given to each patient to discuss the medication formulation of their preference. LAIs should not be reserved as a last line treatment for those who are nonadherent to the oral medications. More recently, there has been increased consideration of the use of LAIs early in the treatment of schizophrenia to prevent relapses and encourage treatment adherence. With the increase in the number of LAIs available for each generic oral medication, many insurance payers have developed preferred formularies or step therapies for LAIs.

APPROACH TO SIDE EFFECT MONITORING

Antipsychotics are well known to cause specific side effects. FGAs, especially high-potency FGAs, are more commonly associated with acute EPS, like parkinsonism, acute dystonia, and akathisia, as well as tardive phenomena, like tardive dyskinesias and dystonia. Drug-induced movement disorders are less common with SGAs, though potent D2 blockers like risperidone still have a significant EPS risk. Even with medications where parkinsonism and dystonias are less common, partial agonism at dopaminergic receptors (e.g., aripiprazole) may lead to akathisia. Regular screening for EPS, especially tardive dyskinesia, is recommended with all antipsychotic medications. Risk factors for both parkinsonism and tardive dyskinesia include being female, mood disorder, and advancing age; dystonias are likely more common in men.[178] In general, prescribing medications less likely to cause EPS and at lower doses is recommended for mitigating EPS risk.

Should EPS occur, treatments are available. Acute dystonias are often quite bothersome and should be treated with anticholinergic medications like benztropine or trihexyphenidyl. Parkinsonism can be approached similarly. Generally, acute dystonias will not reoccur over time, and parkinsonism will abate with continued medication exposure. As such, anticholinergic medications can generally be slowly tapered and withdrawn after a few months.[179] If

parkinsonism occurs after some time on a medication, and the patient is stable, lowering the dose of the medication can be helpful in addressing this side effect. Akathisia can be more challenging to treat, but traditional approaches include propranolol and other beta blockers. Other medications may also be effective and include B6 and mirtazapine.[180] Tardive dystonia is less common but can respond to anticholinergic medication. Botox can also be used in certain cases—for example, in torticollis.[181] The best approach to tardive dyskinesia is prevention rather than treatment. Often, if detected early, dose decreases or medication changes, especially to certain lower-risk SGAs like clozapine, if otherwise clinically appropriate, can be useful to reduce the risk of tardive dyskinesia. Otherwise, maintaining the individual on the current antipsychotic medication if clinically needed and adding a VMAT-2 (vesicular monoamine transporter) inhibitor is now common practice as these medications help block dopamine from accumulating and help with movement-type side effects. VMAT-2 inhibitors have been shown to be generally safe and effective in the treatment of tardive dyskinesia, with medium effect sizes and numbers needed to treat of 2–9, depending on measures used to define response.[182]

Metabolic side effects from antipsychotics are quite common, and prevention is critical. Utilizing most metabolically neutral agents as first-line treatment, when available, can be a powerful way to prevent significant weight gain as well as insulin resistance and hyperlipidemia. Growing evidence supports prescribing metformin when starting olanzapine, clozapine, and potentially other medications with high risk for metabolic side effects. Metformin can help prevent weight gain with these medications and can sometimes help promote weight loss.[183,184] Recent guidelines suggest co-commencement of metformin with clozapine and olanzapine and co-prescribing with other antipsychotic medications should weight gain occur.[185] GLP-1 agonists are being increasingly explored as other options to help patients address antipsychotic-induced weight gain.[186] Careful screening not just for weight gain and hypertension but with serum bloodwork for diabetes screening (HgA1c and fasting glucose) and hyperlipidemia (fasting lipid panel) should be done as per standard guidelines (within 3 months of prescribing, then at 6 months, then yearly). Metabolic risk may be somewhat dose related with certain medications. Treatment should occur in collaboration with a primary care physician and other specialists as indicated. Psychiatrists can be especially helpful in addressing healthy diets and exercise with their patients, who often benefit from consistent messaging and coaching. Counseling on healthy lifestyles should also be given alongside screenings;[187] this is especially critical as patients with schizophrenia are thought to be more sedentary[188] and often eat poorer diets.[189]

Like FGAs, some SGAs also block alpha-1, muscarinic, and histaminergic receptors, which can lead to side effects. Caution should be used in the presence of other commonly prescribed medications that bind to these receptors, as side effects are additive. Orthostatic hypotension can sometimes respond to use of support stockings and increased salt and fluid intake. Should these more conservative measures fail, fludrocortisone may be considered. Antihistaminergic sedation can often be improved with dose reduction or divided dosing. Muscarinic receptor antagonism can lead to anticholinergic side effects, which can be more challenging. These include dry eye, dry mouth, tachycardia, and urinary retention. In some cases, serious side effects like severe constipation leading to intestinal obstruction can occur. Delirium is also a real risk, but milder forms of cognitive impairment associated with anticholinergic side effects can also be problematic and compound preexisting, schizophrenia-associated cognitive deficits. A negative correlation between high anticholinergic medication burden and global cognitive performance, visual or verbal learning, working memory, processing speed, attention, executive

functions, and social functioning has been demonstrated; tapering studies have shown clinically measurable improvements in working memory, verbal learning, and executive function.[190] Eliminating anticholinergic medications is of critical importance. Medications like benztropine, in the absence of parkinsonism or dystonias, can often be safely tapered after several months of continuous use.[191]

Sexual dysfunction is also common in schizophrenia and can be tied to clinical factors of the illness but also can be attributable to antipsychotic medications and binding of serotonergic, adrenergic, and dopaminergic receptors.[192] As noted, prolactin elevation can lead to significant sexual dysfunction as well.[193] Risk of osteoporosis and breast and endometrial cancer with prolactin elevation has occasionally been raised, but evidence to support this is limited.[194] In the treatment of sexual side effects, dose reduction of the antipsychotic can be attempted. Otherwise, addition of dopamine agonists, like bromocriptine or low-dose aripiprazole, can be trialed.[195,196] See **Table 6** for an approach to monitoring various side effects of antipsychotic medications.

Table 6: Monitoring Parameters for Antipsychotic Medications

Category	Monitoring Parameter and Frequency

Metabolic (all patients receiving a second-generation antipsychotic)	• Personal/family history of obesity, diabetes, dyslipidemia, hypertension, cardiovascular disease
	  ○ Annually
	• Body weight and height
	  ○ BMI at 4 weeks, 8 weeks, 12 weeks, and then every 3 months
	• Waist circumference
	  ○ Annually
	• Blood pressure
	  ○ Every visit
	• Fasting blood glucose, A1c
	  ○ 12 weeks and then annually. High-risk patients may require more frequent monitoring
	• Lipid panel
	  ○ 12 weeks and then every 5 years. High-risk patients may require more frequent monitoring

Cardiac (those receiving antipsychotics that are high risk for QTc prolongation, those with cardiac risk factors, those with underlying cardiac disease, > 65 years of age)	• QTc interval (ECG), serum potassium and magnesium ○ Annually, unless there is a significant change in dose of a high- or moderate-risk medication known to cause QTc interval prolongation or medications are added to the regimen that are known to cause clinically significant QTc interval prolongation or symptoms of QTc interval prolongation, which may require more frequent monitoring

Hematological (all patients receiving an antipsychotic medication)	• Complete blood count
	  ○ 4 weeks, 12 weeks and then annually
	• Complete metabolic panel
	  ○ Annually and as clinically indicated

Endocrine and reproductive effects	• Symptoms of hyperprolactinemia (only at baseline if clinically indicated)
	  ○ Screen for symptoms for the first 12 weeks and then annually; Prolactin level if clinically indicated
	• Pregnancy test (women of childbearing age before initiating an antipsychotic medication)
	  ○ As clinically indicated
	• Thyroid function tests (those at risk for developing thyroid disease with depression, receiving quetiapine)
	  ○ 6 weeks and then annually

Ophthalmologic (all patients receiving an antipsychotic medication)	• Clinical history of blurred vision and vision changes ○ Ocular exam every 2 years for patients younger than 40 years; yearly for those older than 40 years

Other effects (part of the differential diagnosis, prior to the initiation of long-term treatment with antipsychotics)	• Rapid plasma reagin, hepatitis C, and human immunodeficiency virus
	  ○ As clinically indicated
	• Drug toxicology, heavy metal screen
	  ○ As clinically indicated
	• CT, MRI
	  ○ As clinically indicated

—Adapted from DeJongh BM. Clinical pearls for the monitoring and treatment of antipsychotic induced metabolic syndrome. Ment Health Clin. 2021;11(6):311-319. doi:10.9740/mhc.2021.11.311

Conclusion

Schizophrenia and related psychotic disorders remain some of the most complex and disabling psychiatric disorders. Yet decades of research have led to meaningful progress in their understanding and treatment. Early psychosis intervention through CSC teams can be instrumental in improving clinical and functional outcomes for evolving schizophrenia. Combining evidence-based psychosocial and pharmacological interventions in a recovery-oriented, person-centered approach enables many individuals with schizophrenia to lead full and meaningful lives. Careful selection and monitoring of antipsychotic medications, including consideration of LAIs, clozapine, and newer agents, are essential components of effective treatment. To optimize outcomes, systems must deliver these interventions in a coordinated and integrated fashion utilizing biopsychosocial frameworks that support holistic recovery.

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