Schizophrenia: advances in pathophysiology, management, and precision medicine

Akira Sawa,[1,2,3] Joshua Chiappelli,[4] Olivia P Hamrah,[5] Nicola G Cascella[1]

[1]Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]Departments of Neuroscience, Biomedical Engineering, Pharmacology, and Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[3]Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
[4]Department of Psychiatry, University of Maryland Baltimore School of Medicine, Baltimore, MD, USA
[5]Department of Psychiatry, Georgetown University Medical Center, Washington, DC, USA
Correspondence to: A Sawa
asawa1@jhmi.edu

Cite this as: *BMJ* 2026;394:e635470
http://dx.doi.org/10.1136/bmj-2026-635470

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally.

ABSTRACT

Schizophrenia is a common and severe mental condition with onset usually in late adolescence and young adulthood. Schizophrenia is caused by a combination of multiple genetic and environmental factors with significant neurodevelopmental implications. Advances in the clinical management of schizophrenia include biological and non-biological treatments. Drug interventions can ameliorate positive symptoms and prevent the progression of disease due to relapses. Non-biological approaches such as psychosocial and cognitive interventions can help functional improvement, relapse prevention, and early stage psychosis management, and new interventions such as neuromodulation and digital health interventions are still under investigation. Despite these advances, novel therapeutic strategies, particularly drugs, are hampered by a biologically heterogeneous population of patients with schizophrenia, a condition defined only by clinical operational criteria. Reconsidering the construct of schizophrenia from the viewpoint of mechanism driven precision medicine will be important, with stratification of patients on the basis of their biological characteristics. The first step towards this goal is to accumulate objective biomarkers for schizophrenia. On the basis of the framework of precision medicine, further advancement in the management of schizophrenia is expected.

Introduction

Schizophrenia is a severe mental condition with its onset usually in late adolescence and young adulthood, and it tends to be chronic.[1] The primary feature of schizophrenia is psychosis, in which individual experiences are distorted from reality with alterations of perceptions and thoughts. Auditory hallucinations, delusions, and disorganised speech and behaviour comprise the cluster of experiences termed "positive" symptoms. In many cases of schizophrenia, major impairments in motivation and emotion are also observed. These are referred to as "negative" symptoms, reflecting the absence of age appropriate behavioural drives. In addition to positive and negative symptoms, several types of cognitive dysfunction are also observed. Together, these symptoms lead to significant decline in social and occupational functioning, with high unemployment rates.

Beyond the psychiatric manifestations, schizophrenia is correlated with premature death. The average lifespan of patients with schizophrenia is about 20 years shorter than that of the general population.[2] Multiple reasons for this premature death may exist, including lifestyle, secondary cardiovascular and metabolic changes elicited by long term drug treatment, and unidentified intrinsic biological vulnerability in patients with schizophrenia. Accelerated ageing and dysregulated ageing associated with biological processes are also suggested in schizophrenia.[3 4] Altogether, schizophrenia is one of the most devasting mental and medical conditions, which results in a major medical and social ramifications.[5]

Given that this condition is clinically defined without any objective biomarker, patients with schizophrenia are biologically heterogeneous. The boundaries between schizophrenia and other psychiatric disorders (particularly bipolar disorder) are also ambiguous, which is the basic motivation of cross disease or transdiagnostic research, such as the effort for Research Domain Criteria and the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) study.[6] The biological heterogeneity of schizophrenia has hampered understanding of the mechanisms of disease and effective drug discovery and development. Although medicines can ameliorate positive symptoms, a third of patients with schizophrenia respond poorly to almost all drugs, defined as treatment resistant cases.[7] Introduction of "precision medicine" in patient care and medical research for schizophrenia is warranted to overcome this dilemma.

This review summarises the latest advances in defining schizophrenia at the biological level with the aim of developing mechanism driven biomarkers. It also underscores the importance of multimodal treatment of schizophrenia including drug therapy, neuromodulatory, and non-biological strategies. Opportunities for future research are also highlighted.

Sources and selection criteria

We did a structured literature search of studies indexed in PubMed and Medline by using the key terms "schizophrenia" and "psychosis" from inception to present, focusing on articles published within the past 10 years (1 January 2015 to 30 November 2025). Additional search terms included "review" and "review article," to include systematic reviews. As this is a narrative review, we placed emphasis on identifying and synthesising the highest quality evidence, giving priority to meta-analyses, randomised controlled trials (RCTs), and systematic reviews. We included only articles published in peer reviewed journals. We excluded case reports, with the exception of seminal or illustrative papers on treatments under investigation. From guidelines across multiple countries, we selected the most comprehensive guidelines that provide clear evidence on approaches to drug therapy, non-drug interventions, and systems of care.

Epidemiology

The lifetime prevalence of schizophrenia has been frequently referred to as being 0.4% (10-90% quantiles 0.18% to 1.16%).[8] The prevalence varies across countries, such as Denmark at 0.27%, England 0.44%, Ireland 0.83%, Italy 0.27%, and the US 0.7%.[9] Epidemiological surveys to identify the prevalence of schizophrenia necessitate a "two stage" epidemiological design, whereby first level screening interviews are followed by a second stage of in-person, clinician administered, semi-structured interviews to reliably diagnose schizophrenia.[10] Meanwhile, the projected lifetime morbid risk includes the proportion of the population with (observed) lifetime ever schizophrenia at the interview plus an additional (projected) proportion of individuals who are non-cases at the time of interview but who are predicted to eventually develop schizophrenia across their lifespan. The median proportion lifetime morbid risk was 0.72%.[8] However, as the distribution of these estimates was right skewed, the mean value was higher than the median (1.19% (standard deviation 1.08)).[11] Accordingly, we can state that the mean lifetime morbid risk of schizophrenia is about 1% (male-to-female ratio approximately 1.4).

Risk factors

Genetic and epidemiological studies suggest that interactions between genetic and environmental factors, particularly those during neural development, play a key role in the aetiology of schizophrenia. Classic twin and adoption studies have suggested that susceptibility for schizophrenia is shared between genetic and environmental factors. The heritability of schizophrenia ranges from 0.61 to 0.81,[12] but the concordance rate of schizophrenia for monozygotic twins ranges from 0.20 to 0.49.[13] Although both genetic and environmental risk factors underlie the aetiology of schizophrenia, the contribution of any single factor is very small. Thus, this is a multifactorial condition.

Environmental factors

Epidemiological studies have associated schizophrenia with late winter or early spring birth, which is usually interpreted in association with in-utero infections.[14] Exposure to genital/reproductive infections and influenza in the first half of pregnancy is a major risk factor for schizophrenia.[15 16] The fact that a variety of infections can increase the risk of schizophrenia suggests a role of the maternal immune system.[17] Maternal immune activation elicits an induction of pro-inflammatory cytokines, such as interleukin-6, which in turn influences fetal brain development.[17] Toxoplasmosis, an infection caused by the parasite *Toxoplasma gondii*, is also known to be a risk for schizophrenia.[18]

Another environmental risk factor during development is malnutrition,[19] which also elicits maternal immune activation. Thus, prenatal or perinatal infection and malnutrition may share a downstream pathophysiological pathway associated with schizophrenia. A recent meta-analysis of cohort and case-control studies found that obstetric complications are associated with greater risk for later development of schizophrenia.[20] Improvement of maternal care and nutrition in at risk mothers may be a meaningful strategy for prevention of schizophrenia.[17 20]

Strong epidemiological evidence shows that cannabis use during adolescence is a major risk factor for the onset of schizophrenia.[21] A longitudinal cohort study found that air pollution was associated with psychotic experiences in adolescence.[22] Like infectious conditions, air pollution can elicit olfactory inflammation, which has also been reported to be present in a subset of patients with schizophrenia.[23] The involvement of autoimmune mechanisms has also been recently highlighted.[24 25] Paediatric traumatic brain injuries are also associated with a risk for later diagnosis of schizophrenia of up to 10 years, as found in a nationwide retrospective cohort study.[26]

In addition to biological factors, several psychosocial environmental factors are also associated with schizophrenia. These may include urban birth, migration, affiliation with an ethnic minority, traumatic experiences, and experience of discrimination.[16 27 28] People immigrating from Africa or the Caribbean and their second generation offspring in the UK have rates of schizophrenia higher than those in the general population.[9] Although urban living as a risk factor for schizophrenia has

been classically interpreted from a psychosocial stress and infectious viewpoint, this may also be associated with air pollution and nasal inflammation. Likewise, investigating how psychosocial environmental risks may be converted into biological factors, which in turn affect brain chemistry and circuitry, is important.

Genetic factors

Recent genome-wide association studies have defined multiple risk loci for schizophrenia.[29 30] Genome-wide efforts of looking for rare genetic and genomic variants have also taken place for schizophrenia.[31] These include studies of copy number variations and exon sequencings. A possible drawback of these genetic studies is the high heterogeneity of samples in their pathophysiology and clinical features under the same diagnostic category named schizophrenia. Although earlier studies indicated the importance of genes involving synaptic function, immune-inflammatory signalling, and epigenetic cascades,[32] more recent and comprehensive studies indicate the significance of the genes with expression mainly in neurons, in particular N-methyl-D-aspartate (NMDA)-type glutamate receptors and associated molecules.[12 31]

Key genetic factors found in schizophrenia have also been underscored in other diagnostic groups, such as bipolar disorder and other neurodevelopmental disorders.[12] This is consistent with the findings from transdiagnostic research linking genetic risk to specific symptoms. To overcome the potential limitation of the small effect size of many risk genes, polygenic risk scores that estimate the overall genetic risk of an individual by combining weighted risks of all risk variants found in genome-wide association studies have been introduced.[33] Furthermore, a way of calculating context specific (pathway guided) polygenic risk scores has been introduced.[34]

Pharmacogenomics holds promise for optimising pharmacodynamics and drug safety.[35] The hope is that the combination of pharmacogenomics with therapeutic drug monitoring will be a valuable clinical management strategy.[36] In genetic studies, a systematic comparison of genetic data from multiple ethnic groups is known to be informative to understand complex human conditions.[37] Although genome-wide genetic studies have been done predominantly with samples from white populations, recent genetic studies have used Asian and African-American samples.[38] In addition to hereditary

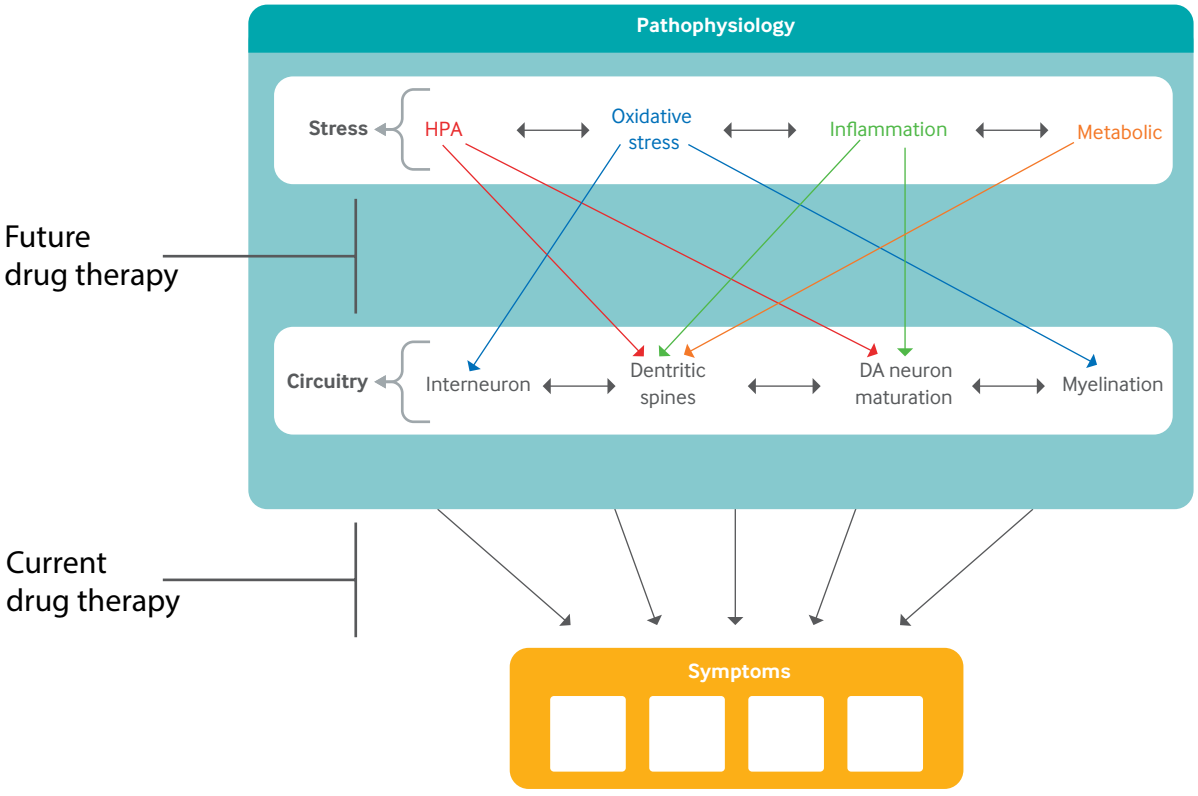

Fig 1 | A working model of schizophrenia pathophysiology and clinical outcomes. Biological investigation with patients with schizophrenia has elucidated relatively common but still diverse pathophysiological mechanisms associated with the disease. These include alterations of neurocircuitry, neurotransmitter, and homeostatic signalling cascades such as immune-inflammatory, redox, and metabolic signalling. Recent basic neurobiological studies have shown mechanistic proofs of how altered immune-inflammatory, redox, and metabolic cascades can affect neurocircuitry and neurotransmitter signalling. Current drugs target an amelioration of aberrant neurotransmission. However, by interfering with the process between the homeostatic signalling cascades and neurocircuitry, development of a novel class of drugs may be possible in the near future. This figure provides a working model focusing on interference with the interplay between the homeostatic signalling cascades and neurocircuitry towards drug discovery for schizophrenia. DA=dopaminergic; HPA=hypothalamic-pituitary-adrenal axis

changes, evidence suggests an involvement of de novo mutations.[12 39] An association between advanced paternal age and a risk of schizophrenia in the offspring may support this notion.[40]

Pathophysiology

Figure 1 summarises the working model based on the observations introduced in this section.

Alteration in neurocircuitry

A classic observation on the brain structure associated with patients with schizophrenia has been an enlargement of lateral ventricles.[41] Although many observations have been reported, the sample size of each study was relatively small. By contrast, the study of structural brain changes in schizophrenia has been aided over the past decade by pooling data from multiple sites. One such effort is the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) initiative.[42] For example, these studies have found a reduction of cortical thickness in schizophrenia in a cross sectional analysis of 9572 participants.[43] A similar reduction, although with a smaller effect size, was found in people at clinical high risk who later converted to psychosis. However, cortical surface area did not predict outcome.[44] Regarding the structural changes in the cortex, progressive changes even several years after the onset of illness have also been reported.[45] Whether these changes reflect a disease progression or secondary effects of drugs is unclear, but the progressive changes may be related to both factors.[46] In addition to the cortical changes, these studies have found a decreased volume of the hippocampus, thalamus, amygdalas, and nucleus accumbens and an increased volume of the pallidum and putamen.[47] In a cross sectional study of 4322 people, schizophrenia was associated with widespread reductions in fractional anisotropy, a measure derived from diffusion tensor imaging that is sensitive to white matter pathology.[48] Reduced fractional anisotropy of white matter is in turn highly correlated with cognitive deficits in patients, particularly processing speed.[49 50] Functional connectivity has been measured by the resting state functional magnetic resonance imaging (MRI) method.[51] Such functional changes may reflect alterations in the synaptic function and may be mediated in part by altered myelination.[52 53]

Alteration in neurotransmission

Although antipsychotic drugs were initially developed in a serendipitous manner, the emergence of contemporary neurobiological and pharmacological methods has revealed a central role of dopaminergic signalling in psychotic disorders. Notable aspects of brain development in adolescence include increased dopaminergic innervation of the prefrontal cortex; these changes may drive normative behavioural changes during adolescence such as increased novelty seeking and risk taking.[54] The primary findings with use of positron emission tomography (PET) to probe the dopamine system in schizophrenia are elevated presynaptic synthesis and release of dopamine. This "hyperdopaminergic" status is observed only in the associative striatum.[55]

Another brain imaging modality using neuromelanin has confirmed the PET imaging data.[56] On a phenomenological level, this abnormal dopaminergic signalling has been proposed to elicit "aberrant salience," in which otherwise neutral stimuli present around the patient's environment are assigned a self-referential value (for example, a passerby becomes a persecutor or a car on the street is there to spy).[57] Consistent with the involvement of dopaminergic signalling in psychotic disorders, people with psychosis who have elevated dopamine synthesis capacity, as determined by PET, show a good response to antipsychotic drugs.[58] Additionally, a composite MRI measure of striatal activity is strongly predictive of response to antipsychotic drugs, providing a potential biomarker to guide treatment.[59]

Despite the evidence implicating dopaminergic dysfunction in core positive symptoms of psychosis, dopamine antagonists, called antipsychotics, do not help all people with psychosis and have little to no benefit for negative symptoms and cognitive deficits. In addition, a third of patients are not responsive to almost all current dopamine antagonist antipsychotics.[7] This has led investigators to probe other neurotransmitter systems. Antagonists of NMDA-type glutamate receptors such as ketamine and phencyclidine reliably produce effects resembling negative and cognitive symptoms, suggesting glutamatergic dysfunction in schizophrenia.[60] Clinical cases resembling psychotic manifestations have been frequently reported as an outcome of an autoantibody against NMDA receptors.[61] Importantly, as described above, many genetic findings have supported the implication of NMDA receptors and associated proteins.[12] Taken together, these findings highlight glutamate as a key neurotransmitter involving the pathophysiology of schizophrenia.

Magnetic resonance spectroscopy has been another prominent imaging tool used to probe the pathophysiology of schizophrenia. By using a stronger magnetic field in a 7 Tesla scanner in research, a significant alteration of multiple metabolites and neurotransmitters has been underscored. These changes include the tissue concentrations of glutamate, N-acetylaspartate, and glutathione. The alteration of glutamate may differ among brain regions,[62 63] which may also be affected by age dependent decline and drugs.[64] N-acetylaspartate concentrations are sensitive to cardiometabolic risk factors, particularly poor glycaemic control,[65 66] providing a potential link between systemic physiological changes and central nervous system (CNS) abnormalities. A reduction of glutathione has been reproducibly reported in schizophrenia,[67] particularly in treatment resistant cases.[68] Given that glutathione can be a reservoir of

synaptic glutamate, this change may also underlie the alteration in glutamate.

In addition to multimodal investigations of patients living with schizophrenia, postmortem brain studies have also taken place very actively in the past decades. A major finding in postmortem studies is a significant change in interneurons in the cerebral cortex, which indicates the involvement of γ-aminobutyric acid (GABA) in the pathophysiology of schizophrenia.[69-71]

Alteration in metabolic, immune/inflammatory, and homeostatic signalling cascades

Given the excess all cause mortality seen in schizophrenia, studies of physiological abnormalities not only inside the brain but also outside of the CNS are also important for understanding the overall pathophysiology of schizophrenia. Systemic abnormalities that have been shown in patients with schizophrenia include immune dysfunction, diminished antioxidant capacity or redox imbalance, poor glycaemic control, and autonomic dysfunction.[72 73] The effect sizes for these abnormalities are comparable to those for changes in brain structure and function in patients with first episode psychosis with minimal antipsychotic exposure.[73]

Chronic inflammation, although mild in magnitude, may play a key role in the pathophysiology of schizophrenia and related psychotic disorders. Notable findings include elevated concentrations of circulating pro-inflammatory molecules such as C reactive protein and interleukins,[74 75] an increased risk for psychotic disorders in people with autoimmune disorders,[76] and the prevalence of genes involved in immune functioning.[32] Alterations in the gut microbiome, possibly through disruption of intestinal epithelial cells, and diminished production of short chain fatty acids may also underlie chronic inflammation.[77] In a birth cohort study of 4500 people, elevated interleukin-6 (but not C reactive protein) concentrations at age 9 was associated with increased risk of having a psychotic disorder at age 18, suggesting that inflammation may not be an artefact of illness or drugs.[78] Elevated concentrations of circulating interleukins (for example, interleukin-6) are elicited by maternal immune activation, a major causative factor, indicating an aetiological and pathophysiological link.[17] This link may be mechanistically explained by a long term blunted response of microglia.[79] Likewise, the regulatory mechanism of immune-inflammatory responses is fine tuned and complex, not simply an up-regulation of astrocytes and microglia. As a result, trials of intervention with anti-inflammatory drugs have not necessarily been successful.[80] In addition, in contrast to illnesses characterised by frank neuroinflammation such as multiple sclerosis, neurological complications of AIDS (neuroAIDS), or Alzheimer's disease, no clear inflammatory CNS lesions have been found in schizophrenia, either through neuroimaging or by postmortem tissue analyses. Meanwhile, more recently, several efforts in more basic neuroscience have elucidated specific brain regions and mechanisms of how immune-inflammatory changes are sensed and can elicit neurocircuitry alterations.[81 82]

Diminished antioxidant capacity or redox imbalance is replicably found in patients with schizophrenia. As described above, multiple reports show a significant reduction of glutathione in the fluid and cells from the blood in patients with schizophrenia.[83] Magnetic resonance spectroscopy studies have shown the reduction of glutathione in the brain (particularly the anterior cingulate cortex) of patients with schizophrenia.[84 85] Alterations of other redox related molecules have also been reported in schizophrenia.[86] Inflammatory changes and redox imbalance are tightly interconnected, suggesting their overall alterations in the pathophysiology of schizophrenia.

Studies on risk for hyperglycaemia, insulin resistance, and type 2 diabetes in patients with schizophrenia have been confounded by the well known metabolic effects of antipsychotic drugs. However, more data are now available for individuals early in the course of illness with little to no exposure to drugs, allowing us to conclude that poor glycaemic control is prominent in schizophrenia independent of drug effects.[87] A longitudinal cohort study in the UK found that high concentrations of fasting insulin in childhood were associated with a greater risk for psychosis in early adulthood.[88] A Danish population level study found a threefold increased risk for diabetes even in patients with schizophrenia not taking antipsychotics.[89] Furthermore, not only is the incidence of diabetes higher in patients with schizophrenia but the incidence of major mental illnesses is higher in people with diabetes in the same large cohort.[90] This bidirectional relation between schizophrenia and diabetes suggests that common pathophysiological mediators associated with insulin resistance may underlie these mental and physical conditions. Furthermore, the impaired insulin signalling was observed in unaffected siblings and patients with first episode psychosis,[91] suggesting that this metabolic change is likely a primary event.

Autonomic dysfunction has long been suspected to be associated with schizophrenia. Evidence for this includes findings of elevated circulating concentrations of catecholamines, elevated resting heart rate, and reduced heart rate variability, all pointing to either sympathetic overactivity or impaired parasympathetic activity.[92] Finally, several reports also suggested an involvement of stress hormones and the hypothalamic-pituitary-adrenal axis in the pathophysiology of schizophrenia, particularly in treatment resistant cases.[93]

Interpretation of pathophysiological data in patients

In the past few decades, major efforts have been made to identify schizophrenia related pathological

changes and alterations of biosignatures in association with its specific clinical manifestations, in the hope of establishing objective biomarkers. We should note that many patients have been exposed to the effects of long term psychotropic drugs, the psychosocial consequences of struggling with a stigmatised and often disabling condition, and high rates of substance use. To tackle this, much effort has been put into studies that recruit patients as early in the course of illness and with as little exposure to drugs as possible. The focus has also shifted towards longitudinal studies that may begin studying individuals even before the start of illness.

Current treatments: biological intervention

Table 1 lists the antipsychotic drugs approved for use in the US.

From the Huhn et al meta-analysis,[100] the above reported antipsychotics were chosen to provide a historical perspective of their development starting with chlorpromazine. They represent the most significant drugs of their class.

Drug treatment: small molecule drugs

Drug treatment is central in biological intervention. The development of chlorpromazine in the early 1950s was a breakthrough for drug treatment of schizophrenia and related psychotic disorders. The rapid development of related drugs with similar effects, now called first generation antipsychotics (FGAs), allowed more people with schizophrenia to be treated as outpatients.[94 95] Studies of dopamine turnover and direct measurements of dopamine receptors established that FGAs block the D2 subtype of dopamine receptors.[94] Later antipsychotics were slightly distinguished from FGAs by a relatively greater ratio of antagonism of 5HT-2A serotonin receptors to antagonism of D2 receptors, termed second generation antipsychotics (SGAs).[95 96]

In terms of clinical effects, the primary distinction between the classes has been in side effect profiles, with SGAs generally less likely to cause involuntary movement deficits called extrapyramidal symptoms than FGAs. However, SGAs frequently cause metabolic problems including hyperlipidaemia and hyperglycaemia.[97] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, an early 18 month multisite randomised trial, discontinuation of olanzapine was significantly less frequent (15%) and occurred later than for perphenazine (25%), risperidone (27%), quetiapine (28%), or ziprasidone (24%); all drugs were associated with improvement in symptom scores but without significant differences between perphenazine and the SGAs.[98] A subsequent

Table 1 | Sample list of antipsychotic drugs approved for use in US by class

Study	Intervention	Study design	Sample size	Treatment duration	Primary outcomes: SMD (95% CI)	Selective side effects
Huhn et al[100]	Phenothiazines: chlorpromazine (CPZ); fluphenazine (FLU)	Meta-analysis	741; 53	3-13 weeks; 3-13 weeks	Overall changes in symptoms: -0.44 (-0.57 to -0.31); -0.24 (-0.62 to 0.13)	Weight gain (mean differences in kg *v* placebo): CPZ (n=308) 2.37 (95% CI 1.43 to 3.32). Sedation: CPZ (n=1078) RR 2.55 (95% CI 2.16 to 2.90); FLU (n=30) RR 1.09 (0.31 to 2.09). Use of anticholinergic agents: CPZ (n=557) RR 2.17 (1.48 to 2.91); FLU (n=30) RR 3.13 (1.99 to 4.16)
Huhn et al[100]	Butyrophenones: haloperidol	Meta-analysis	4400	3-13 weeks	Overall change in symptoms: -0.47 (-0.53 to -0.41)	Weight gain (mean differences in kg *v* placebo) (n=2586): 0.54 (0.15 to 0.95). Sedation (n=3318): RR 1.92 (1.68 to 2.15). Use of anticholinergic agents (n=3549): RR 3.12 (2.74 to 3.50)
Huhn et al[100]	Dibenzoxazepines: loxapine	Meta-analysis	289	3-13 weeks	Overall change in symptoms: -0.45 (-0.63 to -0.26)	Weight gain (mean differences in kg *v* placebo) (n=17): 1.09 (-2.44 to 4.64). Sedation (n=337): RR 2.20 (1.65 to 2.73). Use of anticholinergic agents (n=203): RR 3.13 (1.99 to 4.16)
Huhn et al[100]	Dibenzodiazepines: clozapine	Meta-analysis	270	3-13 weeks	Overall change in symptoms: -0.89 (-1.08 to -0.71)	Weight gain (mean differences in kg *v* placebo) (n=113): 1.89 (0.36 to 3.43). Sedation (n=347): RR 3.02 (2.52 to 3.37). Use of anticholinergic agents (n=144): RR 0.46 (0.19 to 0.88)
Huhn et al[100]	Serotonin-dopamine antagonists: risperidone (RIS); olanzapine (OLA); quetiapine (QUE); paliperidone (PAL)	Meta-analysis	3827; 5602; 3002; 1584	All 3-13 weeks	Overall change in symptoms: -0.55 (-0.62 to -0.48); -0.56 (-0.62 to -0.50); -0.42 (-0.50 to -0.33); -0.49 (-0.59 to -0.39)	Weight gain (mean differences in kg *v* placebo): RIS (n=2521) 1.44 (1.05 to 1.83); OLA (n=4198) 2.78 (2.44 to 3.13); QUE (n=2143) 1.94 (1.42 to 2.45); PAL (n= 1536) 1.49 (0.98 to 2.00). Sedation: RIS (n=2824) RR 2.03 (1.67 to 2.51); OLA (n= 3730) RR 2.78 (2.44 to 3.13); QUE (n= 2726) RR 2.17 (1.93 to 2.40); PAL (n= 1248) RR 1.33 (1.00 to 1.68). Use of anticholinergic agents: RIS (n=2174) RR 1.80 (1.40 to 2.38); OLA (n=3012) RR 1.02 (0.79 to 1.30); QUE (n=2224) RR 1.05 (0.78 to 1.48); PAL (n=1355) RR 1.61 (1.17 to 2.10)
Huhn et al[100]	D2 partial agonists: aripiprazole (ARI); brexpiprazole (BRE); cariprazine (CAR)	Meta-analysis	1926; 1180; 999	Al 3-13 weeks	Overall change in symptoms: -0.41 (-0.50 to -0.32); -0.26 (-0.39 to -0.12); -0.34 (-0.49 to -0.20)	Weight gain (mean differences in kg *v* placebo): ARI (n=1199) 0.48 (-0.05 to 1.01); BRE (n=1113) 0.70 (-0.05 to 1.45); CAR (n=2143) 0.73 (-0.06 to 1.52). Sedation: ARI (n=935) RR 1.46 (1.11 to 1.43); BRE (n= 972) RR 1.64 (0.91 to 2.38); CAR (n= 566) RR 1.12 (0.70 to 1.59). Use of anticholinergic agents: ARI (n=678) RR 1.32 (0.90 to 1.82); BRE (n=598) RR 1.60 (0.80 to 2.63); CAR (n=279) RR 2.21 (1.18 to 3.37)
Kishimoto et al[108]	Long acting injectables	Meta-analysis	7833	≥6 months	Relative risk of hospital admission *v* oral antipsychotic treatment: 0.88 (0.79 to 0.99)	-

CI =confidence interval; RR=risk ratio; SMD=meta-analytic standardised mean difference of overall symptom (positive symptoms) reduction of drug compared with placebo in randomised controlled trials.

meta-analysis of randomised trials suggested that olanzapine may have slightly greater efficacy in total symptom reduction and less discontinuation due to ineffectiveness than other SGAs, although with greater associated weight gain and increases in blood glucose and cholesterol concentrations.[99] However, in the most recent comprehensive meta-analysis of 115 randomised controlled trials, all examined antipsychotics were more effective than placebo for preventing relapse, with no clear difference between antipsychotics (table 1).[100]

In recent years, nationwide cohort studies, including those from northern European countries, have provided unique opportunities to examine real world and long term outcomes associated with antipsychotic treatment. Despite the significant medical risks associated with antipsychotics, maintenance treatment was associated with decreased all cause mortality compared with no antipsychotic treatment in a meta-analysis of cohort studies.[101] Antipsychotic polypharmacy was not associated with a substantially greater risk for non-psychiatric hospital admissions than monotherapy in a nationwide cohort study of 61 889 people.[102] Another analysis of this Finnish nationwide cohort found that antipsychotic polypharmacy was associated with a lower risk for psychiatric readmission to hospital than monotherapy (hazard ratio 0.87-0.93).[103]

Long acting injectables

Patients are often eager to discontinue antipsychotic drugs, and for a small proportion of patients with schizophrenia experiencing their first episode psychosis, sustained remission without medication may be possible. However, rates of relapse of psychosis in patients with schizophrenia without continuing medications are estimated to be more than 60% within one year and up to 95% within three years. Relapses are known to be a major reason for a poor prognosis.[104] Thus, the current recommendation is to continue antipsychotic drugs indefinitely for people with a diagnosis of schizophrenia.[105 106] Nevertheless, poor adherence is still a frequent barrier in the management of schizophrenia.

To overcome this problem, multiple FGAs and SGAs are now available in formulations that can be administered intramuscularly and allow for steady blood concentrations of the drug for periods ranging from two weeks to six months (table 1).[107 108] In a large study of a French national registry (>12 000 people), long acting injectable (LAI) drugs were associated with fewer hospital admissions in patients who were not adherent to oral drugs.[109] Use of LAIs was associated with lower all cause mortality than oral antipsychotics (odds ratio 0.79, 95% confidence interval (CI) 0.66 to 0.95) in a meta-analysis of RCTs and cohort studies including 12 042 patients.[110] An analysis of individual patient data in 688 patients found that relapse rates after discontinuation of drugs were lower for people stabilised on LAIs compared with stabilisation on oral drugs, at least within one year of discontinuation.[111] A review of qualitative studies of patients' perceptions of drugs found that people with schizophrenia tend to recognise the convenience of an LAI compared with oral drugs but can be put off by the logistics of frequent clinic visits for administration, pain from the shots, and the intrusion into their privacy.[112]

Clozapine and treatment resistant cases

As described above, about 30% of patients are defined as treatment resistant cases.[7] Clozapine is unique among antipsychotics, as this is the only drug with a US Food and Drug Administration (FDA) indication for treatment resistant cases.[113] In addition, clozapine remains the only antipsychotic approved by the FDA specifically for reducing the risk of suicidal behaviour in psychotic disorders.[114] A study of two nationwide cohorts including >90 000 patients found that clozapine was the only antipsychotic associated with a significantly lower risk of attempted or completed suicide compared with no medication (hazard ratio 0.64 and 0.66),[115] previously found in a multisite randomised trial. A recent study of population level data from Finland found that the use of clozapine was associated with reduced risk of a second relapse in people with schizophrenia of recent onset compared with any non-clozapine treatment.[116]

Despite the important clinical advantages of clozapine, prescription rates remain low owing to potential adverse effects and logistic challenges in safety monitoring. During the covid-19 pandemic, regulations on clozapine were partially relaxed in the UK, allowing a natural experiment in less frequent blood monitoring for some patients already stabilised on clozapine; no evidence was found of an increased danger of neutropenia being missed.[117] Recently, in the US, the FDA has removed the obligation of prescribers and pharmacies to participate in a risk evaluation and mitigation strategies (REMS) programme for monitoring neutrophil counts.[118] Additionally, absolute neutrophil counts can be obtained reliably from a recently developed method using fingerstick testing that is well suited to in-clinic use, mitigating the challenges posed by frequent blood draws.[119]

Clozapine has been noted to be under-prescribed for people of African descent, in part owing to concern about individuals with benign ethnic neutropenia. However, results of an open label, six month trial of clozapine in people of African ancestry found no increased risk of severe neutropenia, even in those identified as having benign ethnic neutropenia.[120] A common genetic variant ("Duffy-null") is associated with benign ethnic neutropenia and greater risk for neutropenia; testing for this variant may be useful in anticipation of a clozapine trial in people with African or Middle Eastern ancestry.[121] Despite relaxation of the monitoring requirements for agranulocytosis, prescribers must continue to be vigilant for other adverse effects of clozapine, including cardiomyopathy, gastrointestinal hypomotility, and

pneumonia, all of which may be underappreciated as risks and can be fatal.[122]

Electroconvulsive therapy

Electroconvulsive therapy is mainly used in treatment resistant cases of schizophrenia, mostly as a maintenance therapy, or cases with catatonia.[123 124] Although this is widely available in hospital settings with a collaborative team of psychiatrists and anaesthesiologists, safer applications with neurocircuitry based scientific evidence are warranted.

Newer drugs

Cariprazine is a relatively new medicine for schizophrenia, which may also be unique in its higher affinity for dopamine D3 receptors. Given a distinct distribution of D3 receptors from D2 receptors, this drug is expected to elicit fewer extrapyramidal symptoms but maintain a similar level of efficacy against the "hyperdopaminergic" state in schizophrenia.[125]

KarXT (the compound of xanomeline-trospium) is the most recently approved drug for the treatment of schizophrenia. Xanomeline is an agonist for both M1 and M4 muscarinic receptors and does not directly block D2 dopamine receptors, unlike all currently approved treatments for schizophrenia.[126] Historically, xanomeline was tested in the context of Alzheimer's disease, in which major improvements in psychotic symptoms accompanying Alzheimer's disease were observed.[126] Following this unexpected observation, similar antipsychotic activity was observed in a trial for patients with schizophrenia. Nevertheless, adverse effects associated with peripheral muscarinic receptors once precluded a further advancement of the drug development. However, by adding trospium, a peripherally restricted muscarinic receptor antagonist, KarXT was formulated to maintain the efficacy of xanomeline with a major reduction of peripheral tissue driven side effects.[127] As a result, this medicine was finally approved in 2024. In recent clinical trials, KarXT has been effective in reducing positive and negative symptoms and was generally well tolerated.[128] The clinical trials for KarXT are summarised in table 2.[27-129]

As described above, adverse effects elicited by antipsychotics are major problems in managing patient care. Tardive dyskinesia is a movement disorder that can be elicited by the chronic use of antipsychotic drugs, with the risk being higher for FGAs than for SGAs. Because tardive dyskinesia is potentially irreversible, preventive strategies in prescribing, such as favouring SGAs over FGAs and minimising dosages in long term treatment, are crucial. Meanwhile, several vesicular monoamine transporter-2 inhibitors have recently been approved for treatment of movement disorders.[130] Valbenazine has been approved for the treatment of tardive dyskinesia in the US, although deutetrabenazine and tetrabenazine have been approved for use in Huntington's disease.[130] A recent systematic review and network meta-analysis identified deutetrabenazine as a first line treatment along with valbenazine for tardive dyskinesia in schizophrenia.[130] Treatment strategies to mitigate antipsychotic associated weight gain and metabolic syndrome are also an active area of development. Olanzapine combined with samidorphan, a μ-opioid receptor antagonist, led to less weight gain than olanzapine monotherapy in a meta-analysis of RCTs.[131] A meta-analysis of other drugs to limit weight gain found that metformin can be effective.[132] Starting metformin at the same time as initiating a trial of olanzapine or clozapine is now recommended and should be considered when starting other SGAs in individuals with cardiometabolic risk factors.[133]

Current treatments: non-biological interventions

Although drug treatments can provide significant benefit to people living with schizophrenia, drugs alone do not improve many outcomes considered to be crucial components of functional and clinical recovery, such as cognitive performance, social skills, quality of life, employment, and quality of relationships.[134] To close these gaps, increasing research related to non-biological interventions for schizophrenia has shown that, over the spectrum of illness, these interventions are powerful tools

Table 2 | Emerging drug treatment KarXT for schizophrenia

Study	Intervention	Study design	Sample size	Treatment duration	Primary outcomes
Brannan et al[127]	Xanomeline-trospium (KarXT)	Double blind, placebo controlled, 1:1 ratio, up to xanomeline 125 mg and trospium 30 mg	182	5 weeks	Change in PANSS total score from baseline to 5 weeks was -17.4 points with xanomeline-trospium and -5.9 points with placebo (least squares mean difference -11.6 points, 95% CI -16.1 to -7.1; P<0.001)
Kaul et al[128]	Xanomeline-trospium (KarXT)	Randomised, controlled, flexible dose, inpatient, phase 3 trial (EMERGENT -2)	252	5 weeks	Trial met primary endpoint with mean change from baseline to week 5 in PANSS total score that favoured KarXT (-21.2 (SE 1.7) points) versus placebo (-11.6 (1.6) points; least squares mean difference -9.6, -13.9 to -5.2; P<0.0001; Cohen's d effect size 0.61)
Kaul et al[129]	Xanomeline-trospium (KarXT)	Phase 3, multicentre, randomised, double blind, placebo controlled trial in patients with schizophrenia experiencing acute psychosis, at 30 inpatient sites in US and Ukraine (EMERGENT-3)	256	5 weeks	KarXT significantly reduced PANSS total score from baseline to 5 weeks compared with placebo (KarXT -20.6; placebo -12.2; least squares mean difference -8.4, -12.4 to -4.3; P<0.001; Cohen's d effect size 0.60)

CI=confidence interval; PANSS=positive and negative syndrome scale; SE=standard error.

and necessary components of schizophrenia care (table 3). Importantly, the trend towards inclusion of community members and people with lived experience in the design and implementation of this research, often termed public engagement, patient and public involvement and engagement, or community engagement and involvement, further enhances the applicability and overall generalisability of interventions to real world treatment.

Many psychotherapeutic modalities have been studied in schizophrenia. Cognitive behavioural therapy is one of the most studied modalities, with extensive evidence supporting its use in reducing symptom severity in schizophrenia, particularly positive symptoms and social functioning, with a smaller, but still significant effect on reducing negative symptoms.[135] Metacognitive training targets positive symptoms and focuses on psychoeducation, cognitive bias modification, and strategy teaching. Evidence shows that metacognitive training provides significant long term improvement in positive symptoms, particularly delusions, and psychosocial functioning, but has smaller effects on negative symptoms, cognitive biases, self-esteem, and insight.[136] Cognitive remediation is a behavioural training that aims to improve cognitive performance, specifically social cognition and neurocognitive

Table 3 | Evidence based non-biological interventions for schizophrenia

Study	Intervention	Study design	Sample size	Treatment duration	Primary and key secondary outcomes
Bighelli et al[135]	CBTp, psychoeducation	Meta-analysis of RCTs	10 364	1 year	Relapse: CBTp (OR 0.45, 95% CI 0.27 to 0.75), family psychoeducation (0.56, 0.39 to 0.82), patient psychoeducation (0.63, 0.42 to 0.94)
Penney et al[136]	MCT for psychosis	Meta-analysis of RCTs, cohort studies, case reports, and cross sectional studies	1816	1 year	Positive symptoms g=0.50, 95% CI 0.34 to 0.67; delusions g=0.69, 0.45 to 0.93; hallucinations g=0.26, 0.11 to 0.40; cognitive biases g=0.16, 0.03 to 0.29, self-esteem g=0.17, 0.03 to 0.31; negative symptoms g=0.23, 0.10 to 0.37; functioning g=0.41, 0.12 to 0.69
Lejeune et al[137]	Cognitive remediation	Meta-analysis of RCTs	4594	34.86 (SD 23.25) hours, over course of 13.23 (7.63) weeks, with average of 2.84 (1.17) sessions/week	Global cognition g=0.29, 95% CI 0.12 to 0.45; verbal learning k=61, g=0.33; working memory k=62, g=0.32; attention k=35, g=0.28; reasoning and problem solving k=50, g=0.27; processing speed k=52, g=0.20; visual learning k=33, g=0.19. Negative symptoms improved modestly after cognitive remediation training (k=31, g=0.16). Effects on positive symptoms, total symptoms, and depression were non-significant
Kim et al[138]	Psychoeducation	Meta-analysis of RCTs	18 105	1-36 sessions	Family mental health effect size g=1.28, 0.82 to 1.74; knowledge and attitude about schizophrenia g=1.20, 0.82 to 1.59; family burden g=1.13, 0.84 to 1.42; family coping g=0.63, 0.37 to 0.89; family health and wellbeing g=0.57, 0.20 to 0.94; family functioning g=0.49, 0.09 to 0.89
Turner et al[139]	SST	Meta-analysis of RCTs	1437	12 weeks	SST showed superiority over TAU (g=0.3), active controls (g=0.2-0.3), and comparators pooled (g=0.2-0.3) for negative symptoms, and over TAU (g=0.4) and comparators pooled (g=0.3) for general psychopathology
Firth et al[141 142]	Physical exercise	Meta-analysis of controlled trials	385	4-24 weeks	Psychiatric symptoms were significantly reduced by interventions using around 90 min of moderate-to-vigorous exercise per week (SMD 0.72, 95% CI -1.14 to -0.29); exercise significantly improved cognitive domains of working memory (g=0.39; P=0.024; N=7; n=282), social cognition (g=0.71; P=0.002; N=3; n=81), and attention/vigilance (g=0.66; P=0.005; N=3; n=104)
Jambawo et al[143]	Peer support	Meta-analysis of RCTs	5974	-	Peer support interventions significantly improved recovery outcome (SMD=0.29, 95% CI 0.13 to 0.45; P=0.0004) and significantly empowered service users (SMD=0.22, 0.11 to 0.33; P=0.0001) compared with standard care for service users with schizophrenia
de Winter et al[144]	IPS	Meta-analysis of RCTs	3818	-	Increased employment (OR 2.62, 2.37 to 2.89; P<0.01)
Cook et al[145]	Supported employment	RCT	1273	24 months	55% (n=359) of experimental participants achieved competitive employment compared with 34% (n=210) of participants in comparison condition (P<0.001). 51% (n=330) of participants in experimental condition worked for ≥40 hours in ≥1 month compared with 39% (n=245) of those in comparison condition (P<0.001)
Coldwell et al[146]	ACT	Meta-analysis of RCTs and observational studies	5775	-	ACT participants showed 37% (95% CI 18% to 55%) greater reduction in homelessness
Kane et al[149]	CSC (NAVIGATE)	RCT	223	2 years	NAVIGATE participants experienced significantly greater improvement in quality of life than those in community care (group by time interaction P<0.02), with effect size of 0.31
Correll et al[151]	CSC (EIS *v* TAU)	Meta-analysis of RCTs	2176	9-24 months	EIS was associated with better outcomes than TAU at end of treatment for all cause treatment discontinuation (RR 0.70, 95% CI 0.61 to 0.80; P<0.001), ≥1 psychiatric hospital admission (RR 0.74, 0.61 to 0.90; P=0.003), involvement in school or work (RR 1.13, 1.03 to 1.24; P=0.01), total symptom severity (SMD -0.32, -0.47 to -0.17; P<0.001), positive symptom severity (SMD -0.22, -0.32 to -0.11; P<0.001), and negative symptom severity (SMD -0.28, -0.42 to -0.14; P<0.001)
Zheng, et al[154]	CBT for CHR	Meta-analysis of RCTs	1128	6 months	CBTp was significantly more efficacious in reducing rate of transition to psychosis by 6 months (after post hoc sensitivity analysis) (RR 0.44, 0.26 to 0.73)

ACT=assertive community treatment; CBTp=cognitive behavioural therapy for psychosis; CHR=clinical high risk for psychosis; CI=confidence interval; CSC=coordinated specialty care; EIS=early intervention services; IPS=individualised placement and support; MCT=metacognitive training; OR=odds ratio; RCT=randomised controlled trial; RR=relative risk; SD=standard deviation; SMD=standardised mean difference; SST=social skills training; TAU=treatment as usual.

performance, for better overall psychosocial functioning. Although cognitive remediation has been found to improve global cognitive performance and psychosocial functioning, it has not been shown to affect positive or negative symptoms.[137]

Psychoeducation to both patients and families can significantly improve outcomes for patients with schizophrenia. In general, family interventions have been found to be more effective than standard treatment in preventing relapse at 12 months, and family psychoeducation alone was superior to more complex family intervention models.[135] Family interventions can improve family level outcomes such as family mental health, attitude towards schizophrenia diagnosis, family burden, family coping, family health and wellbeing, and family functioning, as well as patient level outcomes including treatment satisfaction and adherence, quality of life, psychiatric symptoms, illness insight, psychosocial functioning, and rates of readmission to hospital.[138]

Skill training is a group or individual modality that most commonly focuses on teaching interpersonal skills to patients with schizophrenia. It has been found to have positive outcomes in proximal measures of skill (for example, role playing) and more distal measures of community functioning,[139] with weak evidence related to relapse prevention.[140] Physical exercise has been found to improve psychopathological outcomes and cognitive performance, specifically aerobic exercise and exercise supervised by an expert, with a dose dependent relation starting at 90 minutes a week for ≥12 weeks.[141 142] Peer support models, which use people who have lived experience of recovery to support those struggling with mental illness, have been found to increase empowerment and recovery outcomes for individuals with schizophrenia.[143] Supported employment services and individualised placement and support can help people with schizophrenia to achieve competitive employment, more work hours, and higher wages, although without showing long term job retention and economic self-sufficiency.[140-145]

Assertive community treatment, in parallel with supported employment services, can be useful for specific populations of patients with schizophrenia. Assertive community treatment, which involves a multidisciplinary team that engages with the patient frequently and within the community, is recommended by the Schizophrenia Patient Outcomes Research Team and significantly reduces hospital admissions and homelessness in people with schizophrenia.[140 146] In a recent study exploring a less resource demanding format, the full assertive community treatment group emerged as superior on personal and social functioning outcomes.

Early intervention for patients with schizophrenia

Identifying and treating schizophrenia early has benefits: less severe symptoms, better overall functioning, and an increased likelihood of remission.[147] Robust evidence supports the use of psychosocial interventions for people in the early phases of schizophrenia clinically, functionally, and in overall cost effectiveness.[134] Coordinated specialty care (CSC) or early intervention services is a multidisciplinary approach to patients with first episode psychosis that emphasises individualised, collaborative, and recovery oriented care and has been widely implemented as the standard of care for these patients in growing numbers worldwide since the 1990s.[148] Shared decision making is central to this approach, integrating evidence based treatment with patient defined goals, preferences, and values. CSC components can vary by programme but typically involve medication management, individual therapy, group therapy, family support, peer support, supported employment services/individualised placement and support, and case management.

The National Institute of Mental Health funded Recovery After an Initial Schizophrenia Episode (RAISE) research initiative brought CSC clinics to communities across the US alongside the Early Psychosis Intervention Network, which links research hubs in the US through a national data coordinating centre.[149 150] Resulting data show that participation in a CSC model improves quality of life, mood, and adherence to treatment; lowers symptom severity; and increases involvement in work and school.[149-152] However, given the variability in the makeup of CSC service packages, evidence on which combination of services and contextual factors most underlie these positive outcomes is lacking. Additionally, with the

Table 4 | Neuromodulation under investigation for schizophrenia

Treatment	Recent developments
Off-label use*	
rTMS	Moderate efficacy for negative symptoms[167]; fMRI navigated rTMS effective for auditory hallucinations[168]
Investigational device exemption†	
ECT	Effective for treatment resistant cases and catatonia[123 124]; generally no cognitive decline when augmenting antipsychotics[123]
tDCS	Shows reduction in auditory verbal hallucination and improving cognition[169]
DBS	Initially used for PD, OCD, and MDD[170]; limited trials; initial improvement with later deterioration[171 172]; subgenual ACC alleviates positive symptoms[172]; SNr DBS shows sustained hallucination reduction[173]
Others (MST, tACS)	Emerging methods; more evidence needed

ACC=anterior cingulate cortex; DBS=deep brain stimulation; DLPFC=dorsolateral prefrontal cortex; ECT=electroconvulsive therapy; fMRI=functional magnetic resonance imaging; MDD=major depressive disorder; MST=magnetic seizure therapy; OCD=obsessive-compulsive disorder; PD=Parkinson's disease; rTMS=repetitive transcranial magnetic resonance; SNr=substantia nigra pars reticulata; tACS=transcranial alternating current stimulation; tDCS=transcranial direct current stimulation.
*Refers to therapeutic approaches not yet officially approved for schizophrenia treatment.
†Indicates therapies permitted for clinical investigation but not yet approved for general clinical use.

implementation of a complex, multidisciplinary model, organisation and resource availability must be considered in real world application and outcomes.[148]

Prevention for people at risk for psychosis

Clinical high risk for psychosis (CHR) or the at-risk mental state is defined as having one or more of three risk syndrome categories: attenuated psychosis, genetic risk with functional decline, and brief limited psychotic symptoms. They are diagnosed with validated semi-structured interviews, and several validated screening tools have also been developed. About 20% of people with CHR will go on to develop schizophrenia within two to three years, and the risk increases with time.[153] A small but growing body of evidence exists for interventions that may alter the course of illness. Cognitive behavioural therapy for psychosis, as described above, has the most robust evidence in reducing attenuated psychotic symptoms in patients with CHR and reducing the rate of transition to schizophrenia.[154] Some evidence also suggests improved psychosocial functioning and psychopathological outcomes with a psychoeducation intervention.[155] Notably, antipsychotic drugs have not been found to be effective in preventing the transition to schizophrenia or improving long term outcomes for people with CHR.[156]

Stigma

Finally, we must consider the impact of stigma and bias in the treatment of schizophrenia, which leads to patients with increased self-stigma, emotional distress, and poorer recovery outcomes.[42 157-159] Regarding bias, studies show that people from racial and ethnic minorities and those with lower socioeconomic status are less likely to receive optimal interventions for serious mental illness. These biases are best reduced by using strategies that tackle bias at the clinician, community, and system level.[160 161]

Emerging treatments

Drug treatments

Although dysfunction of glutamatergic signalling has been underscored as a main pathophysiology of schizophrenia, no drug targeting this signalling has been approved thus far. Continuous efforts are taking place by targeting the group II metabotropic glutamate receptors 2 and 3, D-amino acid oxidase, and glycine transporters. Representative investigational drugs include pomaglumetad for metabotropic glutamate receptors 2 and 3, luvadaxistat for D-amino acid oxidase, and iclepertin for glycine transporter 1.[162 163]

Trace amine associated receptor 1 (TAAR1) has recently been regarded as a promising target for drug discovery and development for schizophrenia, given that a phase 2 clinical trial with ulotaront, a TAAR1 agonist, was successful for schizophrenia.[164] The TAAR1 agonist ameliorates the abnormality of striatal dopamine deficits, such as excess dopamine synthesis capacity and release, at the neuropsychopharmacological level.[162] However, further studies will be needed to assess the potential and application of this medicine.[165 166]

Neuromodulation

Multiple non-invasive approaches, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS), are under clinical investigation (table 4 and table 5).[123] rTMS has been applied to patients with schizophrenia as an off-label treatment. A meta-analysis has shown moderate efficacy in alleviating negative symptoms,[167] whereas functional MRI navigated rTMS was effective for auditory

Table 5 | Studies of neuromodulation for schizophrenia

Study	Intervention	Type of study	Sample size	Primary outcomes
Lorentzen et al[167]	rTMS mainly at DLPFC	Meta-analysis	2633	rTMS showed significant improvement in negative symptoms (SMD 0.41, 95% CI 0.26 to 0.56; P<0.001), corresponding to number needed to treat of ~5
Hua et al[168]	rTMS at left temporoparietal junction	RCT	30	Active rTMS produced significantly greater reductions in Auditory Hallucination Rating Scale scores compared with sham (difference 5.96, 95% CI 3.42 to 8.50; F=4.61, P<0.001; Cohen's d=1.17, 95% CI 0.62 to 1.71). Effects were maintained at 6 week follow-up
Chase et al[169]	tDCS with anode at left DLPFC, cathode at left TPJ or supraorbital region	Narrative review	192	tDCS shows improvements in adaptive and cognitive control (behavioural and neural oscillatory measures); effects on auditory hallucinations are mixed, with some studies showing reductions lasting up to 3 months and others no significant benefit, likely owing to protocol variability
Wang et al[171]	Bilateral DBS at habenula	Single arm clinical trial	2	Case 1 showed improvement during first 7 months (≈8.7% reduction in PANSS negative symptoms and 31.6% reduction in general psychopathology) but deteriorated by 10 months. Case 2 maintained clinical improvement at 12 months (≈53.8% reduction in PANSS positive symptoms, 31.7% in PANSS negative symptoms, and 20.8% in general psychopathology)
Corripio et al[172]	DBS at NAcc/subgenual ACC	Pilot crossover RCT	6	Mean PANSS total score decreased by ~21% during active stimulation. 4/6 (67%) patients met response criteria (≥25% PANSS reduction). Symptoms worsened when stimulation was discontinued. Greater improvement observed with NAcc stimulation than subgenual ACC stimulation
Cascella et al[173]	Bilateral DBS at SNr	Single arm clinical trial	1	Marked improvement in psychotic symptoms, particularly auditory hallucinations, with sustained reductions on clinical rating scales during active stimulation

ACC=anterior cingulate cortex; CI=confidence interval; DBS=deep brain stimulation; DLPFC=dorsolateral prefrontal cortex; NAcc=nucleus accumbens; PANSS=Positive and Negative Syndrome Scale; RCT=randomised controlled trial; rTMS=repetitive transcranial magnetic resonance; SMD=standardised mean difference; SNr=substantia nigra pars reticulata; tDCS=transcranial direct current stimulation; TPJ=temporoparietal junction.

hallucinations.[168] tDCS reportedly reduced auditory verbal hallucinations and improved cognitive functions.[169]

Deep brain stimulation (DBS) is an invasive neuromodulation intervention through surgically implanted electrodes that uses a fixed frequency bi-lobed square wave stimulation of specific subcortical brain regions. The interest in using DBS in schizophrenia has grown out of the success of DBS in Parkinson's disease, as well as its use in treatment resistant obsessive-compulsive disorder and major depressive disorder.[170] Few trials of DBS have been conducted in treatment resistant cases with schizophrenia so far (table 4 and table 5). Two cases of habenular DBS have been reported, with initial improvements followed by deterioration within the year.[171] Seven patients with treatment resistant schizophrenia were randomised to the DBS targeting the nucleus accumbens or subgenual anterior cingulate cortex.[172] More recently, an acute and sustained resolution of auditory verbal hallucination up to six months was observed in a patient with treatment resistant schizophrenia after the stimulation of the substantia nigra pars reticulata.[173]

Psychotherapeutic interventions

Several new psychotherapeutic modalities are being studied for the treatment of schizophrenia. Two examples are Talking with Voices, which covers relationship dynamics between voice hearers and their voices,[174] and compassion focused therapy for psychosis, which emphasises compassionate patterns of thinking to reduce distress related to symptoms of psychosis.[175]Additionally, modalites established for other disorders have been adapted for schizophrenia, such as dialectical behavioural therapy as well as acceptance and commitment therapy.[176]

Digital health interventions

Digital health interventions take advantage of advances in technology to provide low cost and scalable interventions for people with mental illness. Feasible digital health interventions have been developed for people with schizophrenia that may improve health outcomes, particularly when human support is part of the intervention. More research is needed to fully understand the potential benefits of these interventions and how they may be incorporated into standard care models.[177]

Digital technology is useful not only for interventions but also for monitoring of patients, even outside the medical setting. Applications such as wearable devices, which can collect data on patients' behaviours and experiences in real time,[178] are increasingly used to identify signs of symptomatic exacerbations or relapses from early stages.[179]

Guidelines

Many guidelines exist for the management of schizophrenia, including international and country specific guidelines, with few updated within the past five years. Among these guidelines, the UK National Institute for Health and Care Excellence guideline on psychosis and schizophrenia in adults (2014),[180] the American Psychiatric Association practice guideline for the treatment of patients with schizophrenia (2020),[181] the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders (2016),[182] and the Veterans Affairs and Department of Defence (VA/DoD) clinical practice guideline for the management of first episode psychosis and schizophrenia (2023)[183] are the most comprehensive and provide guidance around approach to psychosis, drug therapy, non-drug interventions, and systems of care. Of these, the VA/DoD guideline is the most recently updated and includes visuals such as tables and algorithms for quick clinical reference. The British Association for Psychopharmacology (BAP) guidelines for the pharmacological treatment of schizophrenia (2020)[184] and Canadian Psychiatric Association (CPA) guidelines for pharmacotherapy of schizophrenia in adults (2017)[185] focus specifically on drug interventions, with BAP providing an extensive review of pharmacology across the course of illness and in special populations such as comorbid mood and substance use disorders and CPA commenting on the management of aggression and comorbid depression. The VA/DoD guideline provides more background and consideration of military populations, whereas the European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia (2022)[186] focuses on both drug and non-drug considerations related to the cognitive symptoms of schizophrenia.

International guidelines exist from the World Federation of Societies of Biological Psychiatry and the International College of Neuropsychopharmacology, but these guidelines were last updated in 2013.[187 188] The United Nations High Commissioner for Refugees published a guideline in 2017 on managing schizophrenia in humanitarian non-specialised settings.[189]

Knowledge gaps

A major barrier to the understanding of schizophrenia and its treatment is that this diagnostic construct stems purely from clinical observations. As a result, patients under the diagnostic construct of schizophrenia are biologically heterogeneous.[6 190-192] This hampers a proper understanding of the disease and dramatically enhances the failure rate in clinical trials.[190-192] Thus, we should consider schizophrenia as a multidimensional syndrome that includes varying degrees of positive and negative symptoms, as well as cognitive dysfunction. To close these gaps, we may need to consider sub-stratified groups in schizophrenia based on their biological characteristics. In parallel, we also need to remember that the boundaries between schizophrenia and other psychiatric disorders (particularly bipolar disorder)

are ambiguous, which is the basic motivation of cross-disease or transdiagnostic research. Accordingly, the practical first step towards this goal is to accumulate objective biomarkers for schizophrenia, with which we can stratify schizophrenia into biologically relevant subgroups. The "biotypes" paradigm in the BSNIP study is an innovative example.[6] These efforts may be important to improve the success rate of drug discovery and development, which has been very successful in oncology under the concept of precision medicine.[193]

Conclusion

Both genetic and epidemiological studies of schizophrenia have dramatically advanced in the past two decades. Genetic studies have underscored the significance of neural and synaptic factors as drivers of the disease.[12] Many biological studies that examine living patients with schizophrenia have indicated relatively common but still diverse pathophysiological mechanisms, which include alterations of neurocircuitry, neurotransmitter, and homeostatic signalling cascades such as immune-inflammatory, redox, and metabolic signalling. How the major pathophysiological changes (for example, neurocircuitry and neurotransmitter changes and alterations of homeostatic signalling cascades) are related to each other remains elusive. Recent basic neurobiological studies have shown mechanistic proofs of how altered immune-inflammatory, redox, and metabolic cascades can affect neurocircuitry and neurotransmitter signalling during the developmental trajectory in model animals.[79 194-199] For example, redox imbalance affects the development and functions of neurons, particularly interneurons that are impaired in schizophrenia.[200] Dysfunction of microglia, either hyperactivity or hypoactivity, affects neurocircuitry formation during development.[79 196] In analogy to drug discovery in oncology, we may expect more than one route for success in schizophrenia. As described above, figure 1 shows a working model focusing on the interference with the interplay between the homoostatic signalling cascades and neurocircuitry towards drug discovery for schizophrenia. We hope that mechanism driven, precision medicine based approaches will reshape scientific understanding and advanced management for schizophrenia in coming years.

QUESTIONS FOR FUTURE RESEARCH

- How can we integrate genetic findings, brain imaging data, and multi-omics studies (genomics, transcriptomics, proteomics) to provide convergent evidence on mechanisms of schizophrenia?
- How can we construct biology based subtypes of schizophrenia based on the mechanistic understanding?
- How can we leverage the advances of data science and artificial intelligence?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS MANUSCRIPT

Two patients or patient advocates with schizophrenia reviewed the manuscript and gave constructive feedback, particularly on future perspectives.

This study is supported by National Institutes of Health grants MH-094268, MH-107730, MH-129480, and MH-136297 to AS. We thank Yukiko L Lema for her role in manuscript management and figure/table preparation, Koko Ishizuka for critical reading of the manuscript and manuscript management, and Anruo Shen for table preparation.

Contributors: AS contributed to the overall design, did the literature search, and wrote the article. JC, OPH, and NGC did the literature search and wrote the article. AS is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: AS has acted as a consultant for Sumitomo Pharma and Shimadzu, has collaborated on research for Sumitomo Pharma, and is an associate editor for the American Association for the Advancement of Science.

1 Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 2008;9:947-57. doi:10.1038/nrn2513
2 Laursen TM. Causes of premature mortality in schizophrenia: a review of literature published in 2018. *Curr Opin Psychiatry* 2019;32:388-93. doi:10.1097/YCO.0000000000000530
3 Nguyen TT, Eyler LT, Jeste DV. Systemic Biomarkers of Accelerated Aging in Schizophrenia: A Critical Review and Future Directions. *Schizophr Bull* 2018;44:398-408. doi:10.1093/schbul/sbx069
4 Yang K, Ishizuka K, Tomoda T, et al. Aberrant aging-associated p62 autophagic cascade in biopsied olfactory neuronal cells from patients with psychosis. *Schizophrenia (Heidelb)* 2025;11:68. doi:10.1038/s41537-025-00617-x
5 Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet* 2022;399:473-86. doi:10.1016/S0140-6736(21)01730-X
6 Clementz BA, Sweeney JA, Hamm JP, et al. Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. *Am J Psychiatry* 2016;173:373-84. doi:10.1176/appi.ajp.2015.14091200
7 Nucifora FC, Woznica E, Lee BJ, et al. Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. *Neurobiol Dis* 2019;131:104257. doi:10.1016/j.nbd.2018.08.016
8 McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008;30:67-76. doi:10.1093/epirev/mxn001
9 Messias EL, Chen CY, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. *Psychiatr Clin North Am* 2007;30:323-38. doi:10.1016/j.psc.2007.04.007
10 Phillips MR, Zhang J, Shi Q, et al. Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001-05: an epidemiological survey. *Lancet* 2009;373:2041-53. doi:10.1016/S0140-6736(09)60660-7
11 Leucht S, Siafis S, McGrath JJ, et al. Schizophrenia. *Nat Rev Dis Primers* 2025;11:83. doi:10.1038/s41572-025-00667-6
12 Owen MJ, Bray NJ, Walters JTR, et al. Genomics of schizophrenia, bipolar disorder and major depressive disorder. *Nat Rev Genet* 2025;26:862-77. doi:10.1038/s41576-025-00843-0
13 Hilker R, Helenius D, Fagerlund B, et al. Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. *Biol Psychiatry* 2018;83:492-8. doi:10.1016/j.biopsych.2017.08.017
14 Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol* 2011;93:23-58. doi:10.1016/j.pneurobio.2010.09.003
15 Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry* 2010;167:261-80. doi:10.1176/appi.ajp.2009.09030361
16 Jaaro-Peled H, Sawa A. Neurodevelopmental Factors in Schizophrenia. *Psychiatr Clin North Am* 2020;43:263-74. doi:10.1016/j.psc.2020.02.010
17 Vasistha NA, Sawa A. Prenatal Immune Stress: Its Impact on Brain Development and Neuropsychiatric Disorders. *Annu Rev Neurosci* 2025;48:345-61. doi:10.1146/annurev-neuro-112723-024048

18 Xiao J, Prandovszky E, Kannan G, et al. Toxoplasma gondii: Biological Parameters of the Connection to Schizophrenia. *Schizophr Bull* 2018;44:983-92. doi:10.1093/schbul/sby082
19 Susser E, St Clair D. Prenatal famine and adult mental illness: interpreting concordant and discordant results from the Dutch and Chinese Famines. *Soc Sci Med* 2013;97:325-30. doi:10.1016/j.socscimed.2013.02.049
20 Davies C, Segre G, Estradé A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2020;7:399-410. doi:10.1016/S2215-0366(20)30057-2
21 Gobbi G, Atkin T, Zytynski T, et al. Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 2019;76:426-34. doi:10.1001/jamapsychiatry.2018.4500
22 Newbury JB, Arseneault L, Beevers S, et al. Association of Air Pollution Exposure With Psychotic Experiences During Adolescence. *JAMA Psychiatry* 2019;76:614-23. doi:10.1001/jamapsychiatry.2019.0056
23 Yang K, Hasegawa Y, Bhattarai JP, et al. Inflammation-related pathology in the olfactory epithelium: its impact on the olfactory system in psychotic disorders. *Mol Psychiatry* 2024;29:1453-64. doi:10.1038/s41380-024-02425-8
24 Eaton WW, Byrne M, Ewald H, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry* 2006;163:521-8. doi:10.1176/appi.ajp.163.3.521
25 Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. *Schizophr Res* 2016;176:36-40. doi:10.1016/j.schres.2014.10.007
26 Laaksonen J, Ponkilainen V, Möttönen J, et al. Pediatric traumatic brain injury and later psychotic syndromes in Finland. *Eur J Pediatr* 2025;184:380. doi:10.1007/s00431-025-06224-3
27 van Nierop M, Viechtbauer W, Gunther N, et al. Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. *Psychol Med* 2015;45:1277-88. doi:10.1017/S0033291714002372
28 Anglin DM, Ereshefsky S, Klaunig MJ, et al. From Womb to Neighborhood: A Racial Analysis of Social Determinants of Psychosis in the United States. *Am J Psychiatry* 2021;178:599-610. doi:10.1176/appi.ajp.2020.20071091
29 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511:421-7. doi:10.1038/nature13595
30 Trubetskoy V, Pardiñas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022;604:502-8. doi:10.1038/s41586-022-04434-5
31 Singh T, Poterba T, Curtis D, et al. Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature* 2022;604:509-16. doi:10.1038/s41586-022-04556-w
32 Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci* 2015;18:199-209. doi:10.1038/nn.3922
33 Martin AR, Kanai M, Kamatani Y, et al. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 2019;51:584-91. doi:10.1038/s41588-019-0379-x
34 Choi SW, García-González J, Ruan Y, et al. PRSet: Pathway-based polygenic risk score analyses and software. *PLoS Genet* 2023;19:e1010624. doi:10.1371/journal.pgen.1010624
35 Pardiñas AF, Owen MJ, Walters JTR. Pharmacogenomics: A road ahead for precision medicine in psychiatry. *Neuron* 2021;109:3914-29. doi:10.1016/j.neuron.2021.09.011
36 Brown JT, Bishop JR, Schneiderhan ME. Using pharmacogenomics and therapeutic drug monitoring to guide drug selection and dosing in outpatient mental health comprehensive medication management. *Ment Health Clin* 2020;10:254-8. doi:10.9740/mhc.2020.07.254
37 McClellan JM, Zoghbi AW, Buxbaum JD, et al. An evolutionary perspective on complex neuropsychiatric disease. *Neuron* 2024;112:7-24. doi:10.1016/j.neuron.2023.10.037
38 Ruan Y, Lin YF, Feng YCA, et al. Improving polygenic prediction in ancestrally diverse populations. *Nat Genet* 2022;54:573-80. doi:10.1038/s41588-022-01054-7
39 Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry* 2001;58:361-7. doi:10.1001/archpsyc.58.4.361
40 McGrath JJ, Petersen L, Agerbo E, et al. A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry* 2014;71:301-9. doi:10.1001/jamapsychiatry.2013.4081
41 Weinberger DR, Torrey EF, Neophytides AN, et al. Lateral cerebral ventricular enlargement in chronic schizophrenia. *Arch Gen Psychiatry* 1979;36:735-9. doi:10.1001/archpsyc.1979.01780070013001
42 Thompson PM, Stein JL, Medland SE, et al. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav* 2014;8:153-82. doi:10.1007/s11682-013-9269-5
43 van Erp TGM, Walton E, Hibar DP, et al. Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol Psychiatry* 2018;84:644-54. doi:10.1016/j.biopsych.2018.04.023
44 Jalbrzikowski M, Hayes RA, et al ENIGMA Clinical High Risk for Psychosis Working Group. Association of Structural Magnetic Resonance Imaging Measures With Psychosis Onset in Individuals at Clinical High Risk for Developing Psychosis: An ENIGMA Working Group Mega-analysis. *JAMA Psychiatry* 2021;78:753-66. doi:10.1001/jamapsychiatry.2021.0638
45 Pina-Camacho L, Martinez K, Diaz-Caneja CM, et al. Cortical thinning over two years after first-episode psychosis depends on age of onset. *Schizophrenia (Heidelb)* 2022;8:20. doi:10.1038/s41537-021-00196-7
46 van Haren NEM, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry* 2011;68:871-80. doi:10.1001/archgenpsychiatry.2011.88
47 van Erp TGM, Hibar DP, Rasmussen JM, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry* 2016;21:585. doi:10.1038/mp.2015.118
48 Kelly S, Jahanshad N, Zalesky A, et al. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol Psychiatry* 2018;23:1261-9. doi:10.1038/mp.2017.170
49 Kochunov P, Coyle TR, Rowland LM, et al. Association of White Matter With Core Cognitive Deficits in Patients With Schizophrenia. *JAMA Psychiatry* 2017;74:958-66. doi:10.1001/jamapsychiatry.2017.2228
50 Calarco N, Oliver LD, Joseph M, et al. Multivariate Associations Among White Matter, Neurocognition, and Social Cognition Across Individuals With Schizophrenia Spectrum Disorders and Healthy Controls. *Schizophr Bull* 2023;49:1518-29. doi:10.1093/schbul/sbac216
51 Adhikari BM, Hong LE, Sampath H, et al. Functional network connectivity impairments and core cognitive deficits in schizophrenia. *Hum Brain Mapp* 2019;40:4593-605. doi:10.1002/hbm.24723
52 Friston K, Brown HR, Siemerkus J, et al. The dysconnection hypothesis (2016). *Schizophr Res* 2016;176:83-94. doi:10.1016/j.schres.2016.07.014
53 Valdés-Tovar M, Rodríguez-Ramírez AM, Rodríguez-Cárdenas L, et al. Insights into myelin dysfunction in schizophrenia and bipolar disorder. *World J Psychiatry* 2022;12:264-85. doi:10.5498/wjp.v12.i2.264
54 Larsen B, Luna B. Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neurosci Biobehav Rev* 2018;94:179-95. doi:10.1016/j.neubiorev.2018.09.005
55 McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. *Trends Neurosci* 2019;42:205-20. doi:10.1016/j.tins.2018.12.004
56 Vano LJ, McCutcheon RA, Rutigliano G, et al. Mesostriatal Dopaminergic Circuit Dysfunction in Schizophrenia: A Multimodal Neuromelanin-Sensitive Magnetic Resonance Imaging and [. 18F]-DOPA Positron Emission Tomography Study. *Biol Psychiatry* 2024;96:674-83. doi:10.1016/j.biopsych.2024.06.013
57 Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 2003;160:13-23. doi:10.1176/appi.ajp.160.1.13
58 Jauhar S, Veronese M, Nour MM, et al. Determinants of treatment response in first-episode psychosis: an. 18F-DOPA PET study. *Mol Psychiatry* 2019;24:1502-12. doi:10.1038/s41380-018-0042-4
59 Li A, Zalesky A, Yue W, et al. A neuroimaging biomarker for striatal dysfunction in schizophrenia. *Nat Med* 2020;26:558-65. doi:10.1038/s41591-020-0793-8
60 Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 2012;37:4-15. doi:10.1038/npp.2011.181
61 Guasp M, Rosa-Justicia M, Muñoz-Lopetegi A, et al. Clinical characterisation of patients in the post-acute stage of anti-NMDA receptor encephalitis: a prospective cohort study and comparison with patients with schizophrenia spectrum disorders. *Lancet Neurol* 2022;21:899-910. doi:10.1016/S1474-4422(22)00299-X
62 Merritt K, McCutcheon RA, Aleman A, et al. Variability and magnitude of brain glutamate levels in schizophrenia: a meta and mega-analysis. *Mol Psychiatry* 2023;28:2039-48. doi:10.1038/s41380-023-01991-7
63 Merritt K, McGuire PK, Egerton A, et al. Association of Age, Antipsychotic Medication, and Symptom Severity in Schizophrenia With Proton Magnetic Resonance Spectroscopy Brain Glutamate Level: A Mega-analysis of Individual Participant-

Level Data. *JAMA Psychiatry* 2021;78:667-81. doi:10.1001/jamapsychiatry.2021.0380
64 Wang M, Barker PB, Cascella NG, et al. Longitudinal changes in brain metabolites in healthy controls and patients with first episode psychosis: a 7-Tesla MRS study. *Mol Psychiatry* 2023;28:2018-29. doi:10.1038/s41380-023-01969-5
65 Chiappelli J, Rowland LM, Wijtenburg SA, et al. Cardiovascular risks impact human brain N-acetylaspartate in regionally specific patterns. *Proc Natl Acad Sci U S A* 2019;116:25243-9. doi:10.1073/pnas.1907730116
66 Wu GY, Zhang Q, Wu JL, et al. Changes in cerebral metabolites in type 2 diabetes mellitus: A meta-analysis of proton magnetic resonance spectroscopy. *J Clin Neurosci* 2017;45:9-13. doi:10.1016/j.jocn.2017.07.017
67 Palaniyappan L, Park MTM, Jeon P, et al. Is There a Glutathione Centered Redox Dysregulation Subtype of Schizophrenia? *Antioxidants (Basel)* 2021;10:1703. doi:10.3390/antiox10111703
68 Yang K, Longo L, Narita Z, et al. A multimodal study of a first episode psychosis cohort: potential markers of antipsychotic treatment resistance. *Mol Psychiatry* 2022;27:1184-91. doi:10.1038/s41380-021-01331-7
69 Heckers S, Konradi C. GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. *Schizophr Res* 2015;167:4-11. doi:10.1016/j.schres.2014.09.041
70 Feber L, Peter NL, Chiocchia V, et al. Antipsychotic Drugs and Cognitive Function: A Systematic Review and Network Meta-Analysis. *JAMA Psychiatry* 2025;82:47-56. doi:10.1001/jamapsychiatry.2024.2890
71 Volk DW, Lewis DA. Early developmental disturbances of cortical inhibitory neurons: contribution to cognitive deficits in schizophrenia. *Schizophr Bull* 2014;40:952-7. doi:10.1093/schbul/sbu111
72 Landek-Salgado MA, Faust TE, Sawa A. Molecular substrates of schizophrenia: homeostatic signaling to connectivity. *Mol Psychiatry* 2016;21:10-28. doi:10.1038/mp.2015.141
73 Pillinger T, D'Ambrosio E, McCutcheon R, et al. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *Mol Psychiatry* 2019;24:776-94. doi:10.1038/s41380-018-0058-9
74 Fernandes BS, Steiner J, Bernstein HG, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol Psychiatry* 2016;21:554-64. doi:10.1038/mp.2015.87
75 Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011;70:663-71. doi:10.1016/j.biopsych.2011.04.013
76 Benros ME, Nielsen PR, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry* 2011;168:1303-10. doi:10.1176/appi.ajp.2011.11030516
77 Kelly JR, Minuto C, Cryan JF, et al. The role of the gut microbiome in the development of schizophrenia. *Schizophr Res* 2021;234:4-23. doi:10.1016/j.schres.2020.02.010
78 Khandaker GM, Pearson RM, Zammit S, et al. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA Psychiatry* 2014;71:1121-8. doi:10.1001/jamapsychiatry.2014.1332
79 Hayes LN, An K, Carloni E, et al. Prenatal immune stress blunts microglia reactivity, impairing neurocircuitry. *Nature* 2022;610:327-34. doi:10.1038/s41586-022-05274-z
80 Jeppesen R, Christensen RHB, Pedersen EMJ, et al. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders - A comprehensive systematic review and meta-analysis. *Brain Behav Immun* 2020;90:364-80. doi:10.1016/j.bbi.2020.08.028
81 Lee B, Kwon JT, Jeong Y, et al. Inflammatory and anti-inflammatory cytokines bidirectionally modulate amygdala circuits regulating anxiety. *Cell* 2025;188:2190-2202.e15. doi:10.1016/j.cell.2025.03.005
82 Zhu XA, Starosta S, Ferrer M, et al. A neuroimmune circuit mediates cancer cachexia-associated apathy. *Science* 2025;388:eadm8857. doi:10.1126/science.adm8857
83 Perkins DO, Jeffries CD, Do KQ. Potential Roles of Redox Dysregulation in the Development of Schizophrenia. *Biol Psychiatry* 2020;88:326-36. doi:10.1016/j.biopsych.2020.03.016
84 Murray AJ, Humpston CS, Wilson M, et al. Measurement of brain glutathione with magnetic Resonance spectroscopy in Schizophrenia-Spectrum disorders - A systematic review and Meta-Analysis. *Brain Behav Immun* 2024;115:3-12. doi:10.1016/j.bbi.2023.09.017
85 Das TK, Javadzadeh A, Dey A, et al. Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione. *Prog Neuropsychopharmacol Biol Psychiatry* 2019;91:94-102. doi:10.1016/j.pnpbp.2018.08.006
86 Rambaud V, Marzo A, Chaumette B. Oxidative Stress and Emergence of Psychosis. *Antioxidants (Basel)* 2022;11:1870. doi:10.3390/antiox11101870
87 Pillinger T, Beck K, Gobjila C, et al. Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 2017;74:261-9. doi:10.1001/jamapsychiatry.2016.3803
88 Perry BI, Stochl J, Upthegrove R, et al. Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations With Risks of Psychosis and Depression in Young Adults. *JAMA Psychiatry* 2021;78:416-25. doi:10.1001/jamapsychiatry.2020.4180
89 Rajkumar AP, Horsdal HT, Wimberley T, et al. Endogenous and Antipsychotic-Related Risks for Diabetes Mellitus in Young People With Schizophrenia: A Danish Population-Based Cohort Study. *Am J Psychiatry* 2017;174:686-94. doi:10.1176/appi.ajp.2016.16040442
90 Takayanagi Y, Ishizuka K, Laursen TM, et al. From population to neuron: exploring common mediators for metabolic problems and mental illnesses. *Mol Psychiatry* 2021;26:3931-42. doi:10.1038/s41380-020-00939-5
91 Chouinard VA, Henderson DC, Dalla Man C, et al. Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis. *Mol Psychiatry* 2019;24:1513-22. doi:10.1038/s41380-018-0045-1
92 Stogios N, Gdanski A, Gerretsen P, et al. Autonomic nervous system dysfunction in schizophrenia: impact on cognitive and metabolic health. *NPJ Schizophr* 2021;7:22. doi:10.1038/s41537-021-00151-6
93 Mondelli V, Ciufolini S, Belvederi Murri M, et al. Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis. *Schizophr Bull* 2015;41:1162-70. doi:10.1093/schbul/sbv028
94 Sawa A, Snyder SH. Schizophrenia: neural mechanisms for novel therapies. *Mol Med* 2003;9:3-9. .
95 Leucht S, Priller J, Davis JM. Antipsychotic Drugs: A Concise Review of History, Classification, Indications, Mechanism, Efficacy, Side Effects, Dosing, and Clinical Application. *Am J Psychiatry* 2024;181:865-78. doi:10.1176/appi.ajp.20240738
96 Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* 2011;11:59-67. doi:10.1016/j.coph.2011.02.007
97 Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010;123:225-33. doi:10.1016/j.schres.2010.07.012
98 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23. doi:10.1056/NEJMoa051688
99 Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2010;2010:CD006654. doi:10.1002/14651858.CD006654.pub2
100 Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019;394:939-51. doi:10.1016/S0140-6736(19)31135-3
101 Correll CU, Solmi M, Croatto G, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry* 2022;21:248-71. doi:10.1002/wps.20994
102 Taipale H, Tanskanen A, Tiihonen J. Safety of Antipsychotic Polypharmacy Versus Monotherapy in a Nationwide Cohort of 61,889 Patients With Schizophrenia. *Am J Psychiatry* 2023;180:377-85. doi:10.1176/appi.ajp.20220446
103 Tiihonen J, Taipale H, Mehtälä J, et al. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA Psychiatry* 2019;76:499-507. doi:10.1001/jamapsychiatry.2018.4320
104 Emsley R, Chiliza B, Asmal L, et al. The nature of relapse in schizophrenia. *BMC Psychiatry* 2013;13:50. doi:10.1186/1471-244X-13-50
105 Hui CLM, Honer WG, Lee EHM, et al. Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. *Lancet Psychiatry* 2018;5:432-42. doi:10.1016/S2215-0366(18)30090-7
106 Zipursky RB, Odejayi G, Agid O, et al. You say •schizophrenia• and I say •psychosis•: Just tell me when I can come off this medication. *Schizophr Res* 2020;225:39-46. doi:10.1016/j.schres.2020.02.009
107 Misawa F, Kishimoto T, Hagi K, et al. Safety and tolerability of long-acting injectable versus oral antipsychotics: A meta-analysis of randomized controlled studies comparing the same

antipsychotics. *Schizophr Res* 2016;176:220-30. doi:10.1016/j.schres.2016.07.018
108 Kishimoto T, Hagi K, Kurokawa S, et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry* 2021;8:387-404. doi:10.1016/S2215-0366(21)00039-0
109 Boyer L, Falissard B, Nuss P, et al. Real-world effectiveness of long-acting injectable antipsychotic treatments in a nationwide cohort of 12,373 patients with schizophrenia-spectrum disorders. *Mol Psychiatry* 2023;28:3709-16. doi:10.1038/s41380-023-02175-z
110 Aymerich C, Salazar de Pablo G, Pacho M, et al. All-cause mortality risk in long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis. *Mol Psychiatry* 2025;30:263-71. doi:10.1038/s41380-024-02694-3
111 Schoretsanitis G, Kane JM, Correll CU, et al. Predictors of Lack of Relapse After Random Discontinuation of Oral and Long-acting Injectable Antipsychotics in Clinically Stabilized Patients with Schizophrenia: A Re-analysis of Individual Participant Data. *Schizophr Bull* 2022;48:296-306. doi:10.1093/schbul/sbab091
112 Aprile SF, Rodolico A, Di Francesco A, et al. Oral versus long-acting injectable antipsychotics in schizophrenia spectrum disorders: A systematic review of patients' subjective experiences. *Psychiatry Res* 2025;348:116460. doi:10.1016/j.psychres.2025.116460
113 Nucifora FC, Mihaljevic M, Lee BJ, et al. Clozapine as a Model for Antipsychotic Development. *Neurotherapeutics* 2017;14:750-61. doi:10.1007/s13311-017-0552-9
114 Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003;60:82-91. doi:10.1001/archpsyc.60.1.82
115 Taipale H, Lähteenvuo M, Tanskanen A, et al. Comparative Effectiveness of Antipsychotics for Risk of Attempted or Completed Suicide Among Persons With Schizophrenia. *Schizophr Bull* 2021;47:23-30. doi:10.1093/schbul/sbaa111
116 Taipale H, Tanskanen A, Howes O, et al. Comparative effectiveness of antipsychotic treatment strategies for relapse prevention in first-episode schizophrenia in Finland: a population-based cohort study. *Lancet Psychiatry* 2025;12:122-30. doi:10.1016/S2215-0366(24)00366-3
117 Thai H, Preobrazenski N, Hsieh T, et al. Evaluating Reduced Blood Monitoring Frequency and the Detection of Hematological Abnormalities in Clozapine-Treated Patients With Schizophrenia: A Chart Review Study From the COVID-19 Pandemic. *Schizophr Bull* 2025;51:493-500. doi:10.1093/schbul/sbae113
118 Kameg B. Elimination of the clozapine risk evaluation and mitigation strategy (REMS) - Improving access to care for those with treatment-refractory schizophrenia. *Arch Psychiatr Nurs* 2025;55:151862. doi:10.1016/j.apnu.2025.151862
119 Kelly DL, Ponomareva OY, Mackowick M, et al. Feasibility and patient-reported satisfaction using a novel point-of-care fingerstick method for monitoring absolute neutrophil count for clozapine. *Ann Clin Psychiatry* 2021;33:116-23. doi:10.12788/acp.0029
120 Kelly DL, Glassman M, Wonodi I, et al. Clozapine and neutrophil response in patients of African descent: A six-month, multinational, prospective, open-label clinical trial. *Schizophr Res* 2024;268:312-22. doi:10.1016/j.schres.2023.08.002
121 Legge SE, Pardiñas AF, Helthuis M, et al. A genome-wide association study in individuals of African ancestry reveals the importance of the Duffy-null genotype in the assessment of clozapine-related neutropenia. *Mol Psychiatry* 2019;24:328-37. doi:10.1038/s41380-018-0335-7
122 Partanen JJ, Häppölä P, Kämpe A, et al. High Burden of Ileus and Pneumonia in Clozapine-Treated Individuals With Schizophrenia: A Finnish 25-Year Follow-Up Register Study. *Am J Psychiatry* 2024;181:879-92. doi:10.1176/appi.ajp.20230744
123 Neufeld NH, Blumberger DM. An Update on the Use of Neuromodulation Strategies in the Treatment of Schizophrenia. *Am J Psychiatry* 2025;182:332-40. doi:10.1176/appi.ajp.20250068
124 Kritzer MD, Peterchev AV, Camprodon JA. Electroconvulsive Therapy: Mechanisms of Action, Clinical Considerations, and Future Directions. *Harv Rev Psychiatry* 2023;31:101-13. doi:10.1097/HRP.0000000000000365
125 Patel A, Patel A, Patel D, et al. Mini Review on Cariprazine: A Promising Antipsychotic Agent. *CNS Neurol Disord Drug Targets* 2023;22:226-36. doi:10.2174/1871527321666220324121935
126 Smith CM, Augustine MS, Dorrough J, et al. Xanomeline-trospium (Cobenfy. TM) for Schizophrenia: A Review of the Literature. *Clin Psychopharmacol Neurosci* 2025;23:2-14. doi:10.9758/cpn.24.1253
127 Brannan SK, Sawchak S, Miller AC, et al. Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia. *N Engl J Med* 2021;384:717-26. doi:10.1056/NEJMoa2017015
128 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;403:160-70. doi:10.1016/S0140-6736(23)02190-6
129 Kaul I, Sawchak S, Walling DP, et al. Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry* 2024;81:749-56. doi:10.1001/jamapsychiatry.2024.0785
130 Solmi M, Pigato G, Kane JM, et al. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 2018;12:1215-38. doi:10.2147/DDDT.S133205
131 Correll CU, Doane MJ, McDonnell D, et al. Olanzapine/Samidorphan Effects on Weight Gain: An Individual Patient Data Meta-Analysis of Phase 2 and 3 Randomized Double-Blind Studies. *J Clin Psychiatry* 2025;86:24m15526. doi:10.4088/JCP.24m15526
132 Agarwal SM, Stogios N, Faulkner GEJ, et al. Pharmacological Interventions for the Prevention of Antipsychotic-Induced Weight Gain in People With Schizophrenia: A Cochrane Systematic Review and Meta-Analysis. *Schizophr Bull* 2023;49:833-5. doi:10.1093/schbul/sbad037
133 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* 2025;51:1193-205. doi:10.1093/schbul/sbae205
134 Barlati S, Nibbio G, Vita A. Evidence-based psychosocial interventions in schizophrenia: a critical review. *Curr Opin Psychiatry* 2024;37:131-9. doi:10.1097/YCO.0000000000000925
135 Bighelli I, Rodolico A, García-Mieres H, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry* 2021;8:969-80. doi:10.1016/S2215-0366(21)00243-1
136 Penney D, Sauvé G, Mendelson D, et al. Immediate and Sustained Outcomes and Moderators Associated With Metacognitive Training for Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 2022;79:417-29. doi:10.1001/jamapsychiatry.2022.0277
137 Lejeune JA, Northrop A, Kurtz MM. A Meta-analysis of Cognitive Remediation for Schizophrenia: Efficacy and the Role of Participant and Treatment Factors. *Schizophr Bull* 2021;47:997-1006. doi:10.1093/schbul/sbab022
138 Kim SH, Park S. Effectiveness of family interventions for patients with schizophrenia: A systematic review and meta-analysis. *Int J Ment Health Nurs* 2023;32:1598-615. doi:10.1111/inm.13198
139 Turner DT, McGlanaghy E, Cuijpers P, et al. A Meta-Analysis of Social Skills Training and Related Interventions for Psychosis. *Schizophr Bull* 2018;44:475-91. doi:10.1093/schbul/sbx146
140 Dixon LB, Dickerson F, Bellack AS, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull* 2010;36:48-70. doi:10.1093/schbul/sbp115
141 Firth J, Cotter J, Elliott R, et al. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol Med* 2015;45:1343-61. doi:10.1017/S0033291714003110
142 Firth J, Stubbs B, Rosenbaum S, et al. Aerobic Exercise Improves Cognitive Functioning in People With Schizophrenia: A Systematic Review and Meta-Analysis. *Schizophr Bull* 2017;43:546-56. doi:10.1093/schbul/sbw115
143 Jambawo SM, Owolewa R, Jambawo TT. The effectiveness of peer support on the recovery and empowerment of people with schizophrenia: A systematic review and meta-analysis. *Schizophr Res* 2024;274:270-9. doi:10.1016/j.schres.2024.10.006
144 de Winter L, Couwenbergh C, van Weeghel J, et al. Who benefits from individual placement and support? A meta-analysis. *Epidemiol Psychiatr Sci* 2022;31:e50. doi:10.1017/S2045796022000300
145 Cook JA, Lehman AF, Drake R, et al. Integration of psychiatric and vocational services: a multisite randomized, controlled trial of supported employment. *Am J Psychiatry* 2005;162:1948-56. doi:10.1176/appi.ajp.162.10.1948
146 Coldwell CM, Bender WS. The effectiveness of assertive community treatment for homeless populations with severe mental illness: a meta-analysis. *Am J Psychiatry* 2007;164:393-9. doi:10.1176/ajp.2007.164.3.393
147 Penttilä M, Jääskeläinen E, Hirvonen N, et al. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2014;205:88-94. doi:10.1192/bjp.bp.113.127753
148 Read H, Kohrt BA. The History of Coordinated Specialty Care for Early Intervention in Psychosis in the United States: A Review of Effectiveness, Implementation, and Fidelity. *Community Ment Health J* 2022;58:835-46. doi:10.1007/s10597-021-00891-w
149 Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment

Program. *Am J Psychiatry* 2016;173:362-72. doi:10.1176/appi.ajp.2015.15050632
150 Kane JM, Schooler NR, Marcy P, et al. The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. *J Clin Psychiatry* 2015;76:240-6. doi:10.4088/JCP.14m09289
151 Correll CU, Galling B, Pawar A, et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Psychiatry* 2018;75:555-65. doi:10.1001/jamapsychiatry.2018.0623
152 Robinson DG, Schooler NR, Marcy P, et al. Outcomes During and After Early Intervention Services for First-Episode Psychosis: Results Over 5 Years From the RAISE-ETP Site-Randomized Trial. *Schizophr Bull* 2022;48:1021-31. doi:10.1093/schbul/sbac053
153 Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry* 2012;69:220-9. doi:10.1001/archgenpsychiatry.2011.1472
154 Zheng Y, Xu T, Zhu Y, et al. Cognitive Behavioral Therapy for Prodromal Stage of Psychosis-Outcomes for Transition, Functioning, Distress, and Quality of Life: A Systematic Review and Meta-analysis. *Schizophr Bull* 2022;48:8-19. doi:10.1093/schbul/sbab044
155 Herrera SN, Sarac C, Phili A, et al. Psychoeducation for individuals at clinical high risk for psychosis: A scoping review. *Schizophr Res* 2023;252:148-58. doi:10.1016/j.schres.2023.01.008
156 Caballero N, Machiraju S, Diomino A, et al. Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis. *Curr Psychiatry Rep* 2023;25:683-98. doi:10.1007/s11920-023-01456-2
157 Busch AB, Lehman AF, Goldman H, et al. Changes over time and disparities in schizophrenia treatment quality. *Med Care* 2009;47:199-207. doi:10.1097/MLR.0b013e31818475b7
158 Reininghaus U, Reinhold AS, Priebe S, et al. Toward Equitable Interventions in Public Mental Health: A Review. *JAMA Psychiatry* 2024;81:1270-5. doi:10.1001/jamapsychiatry.2024.3206
159 Wood L, Byrne R, Burke E, et al. The impact of stigma on emotional distress and recovery from psychosis: The mediatory role of internalised shame and self-esteem. *Psychiatry Res* 2017;255:94-100. doi:10.1016/j.psychres.2017.05.016
160 Olbert CM, Nagendra A, Buck B. Meta-analysis of Black vs. White racial disparity in schizophrenia diagnosis in the United States: Do structured assessments attenuate racial disparities? *J Abnorm Psychol* 2018;127:104-15. doi:10.1037/abn0000309
161 Tsang HWH, Ching SC, Tang KH, et al. Therapeutic intervention for internalized stigma of severe mental illness: A systematic review and meta-analysis. *Schizophr Res* 2016;173:45-53. doi:10.1016/j.schres.2016.02.013
162 Howes OD, Dawkins E, Lobo MC, et al. New Drug Treatments for Schizophrenia: A Review of Approaches to Target Circuit Dysfunction. *Biol Psychiatry* 2024;96:638-50. doi:10.1016/j.biopsych.2024.05.014
163 Moran PM, Granger KT. IUPHAR review: Moving beyond dopamine-based therapeutic strategies for schizophrenia. *Pharmacol Res* 2025;216:107727. doi:10.1016/j.phrs.2025.107727
164 Koblan KS, Kent J, Hopkins SC, et al. A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *N Engl J Med* 2020;382:1497-506. doi:10.1056/NEJMoa1911772
165 Jarab A, Al-Qerem W, Khdour A, et al. Novel pharmaceutical treatment approaches for schizophrenia: a systematic literature review. *Eur J Clin Pharmacol* 2025;81:525-41. doi:10.1007/s00228-025-03809-7
166 Smith KA, Boyce N, Chevance A, et al. Triangulating evidence from the GALENOS living systematic review on trace amine-associated receptor 1 (TAAR1) agonists in psychosis. *Br J Psychiatry* 2025;226:162-70. doi:10.1192/bjp.2024.237
167 Lorentzen R, Nguyen TD, McGirr A, et al. The efficacy of transcranial magnetic stimulation (TMS) for negative symptoms in schizophrenia: a systematic review and meta-analysis. *Schizophrenia (Heidelb)* 2022;8:35. doi:10.1038/s41537-022-00248-6
168 Hua Q, Wang L, He K, et al. Repetitive Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations in Schizophrenia: A Randomized Clinical Trial. *JAMA Netw Open* 2024;7:e2444215. doi:10.1001/jamanetworkopen.2024.44215
169 Chase HW, Boudewyn MA, Carter CS, et al. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Mol Psychiatry* 2020;25:397-407. doi:10.1038/s41380-019-0499-9
170 Polosan M, Figee M. Electrical deep neuromodulation in psychiatry. *Int Rev Neurobiol* 2021;159:89-110. doi:10.1016/bs.irn.2021.06.007
171 Wang Y, Zhang C, Zhang Y, et al. Habenula deep brain stimulation for intractable schizophrenia: a pilot study. *Neurosurg Focus* 2020;49:E9. doi:10.3171/2020.4.FOCUS20174
172 Corripio I, Roldán A, McKenna P, et al. Target selection for deep brain stimulation in treatment resistant schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2022;112:110436. doi:10.1016/j.pnpbp.2021.110436
173 Cascella N, Butala AA, Mills K, et al. Deep Brain Stimulation of the Substantia Nigra Pars Reticulata for Treatment-Resistant Schizophrenia: A Case Report. *Biol Psychiatry* 2021;90:e57-9. doi:10.1016/j.biopsych.2021.03.007
174 Longden E, Corstens D, Bowe S, et al. A psychological intervention for engaging dialogically with auditory hallucinations (Talking With Voices): A single-site, randomised controlled feasibility trial. *Schizophr Res* 2022;250:172-9. doi:10.1016/j.schres.2022.11.007
175 Heriot-Maitland C. Position paper - CFT for psychosis. *Psychol Psychother* 2024;97:59-73. doi:10.1111/papt.12490
176 Jolley S, Johns LC, O'Donoghue E, et al. Group acceptance and commitment therapy for patients and caregivers in psychosis services: Feasibility of training and a preliminary randomized controlled evaluation. *Br J Clin Psychol* 2020;59:524-51. doi:10.1111/bjc.12265
177 Arnautovska U, Trott M, Vitangcol KJ, et al. Efficacy of User Self-Led and Human-Supported Digital Health Interventions for People With Schizophrenia: A Systematic Review and Meta-Analysis. *Schizophr Bull* 2025;51:1402-16. doi:10.1093/schbul/sbae143
178 Hau C, Xia W, Ryan S, et al. Smartphone monitoring and digital phenotyping apps for schizophrenia: A review of the academic literature. *Schizophr Res* 2025;281:237-48. doi:10.1016/j.schres.2025.05.019
179 Cohen A, Naslund JA, Chang S, et al. Relapse prediction in schizophrenia with smartphone digital phenotyping during COVID-19: a prospective, three-site, two-country, longitudinal study. *Schizophrenia (Heidelb)* 2023;9:6. doi:10.1038/s41537-023-00332-5
180 Kuipers E, Yesufu-Udechuku A, Taylor C, et al. Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. *BMJ* 2014;348:g1173. doi:10.1136/bmj.g1173
181 Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry* 2020;177:868-72. doi:10.1176/appi.ajp.2020.177901
182 Galletly C, Castle D, Dark F, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Aust N Z J Psychiatry* 2016;50:410-72. doi:10.1177/0004867416641195
183 Niv N, Issa F, Goldberg R, et al. Psychosocial Management of First-Episode Psychosis and Schizophrenia: Synopsis of the US Department of Veterans Affairs and US Department of Defense Clinical Practice Guidelines. *Schizophr Bull* 2025;51:949-68. doi:10.1093/schbul/sbaf035
184 Barnes TR, Drake R, Paton C, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2020;34:3-78. doi:10.1177/0269881119889296
185 Remington G, Addington D, Honer W, et al. Guidelines for the Pharmacotherapy of Schizophrenia in Adults. *Can J Psychiatry* 2017;62:604-16. doi:10.1177/0706743717720448
186 Khorikian-Ghazari N, Lorenz C, Güler D, et al. Guideline for schizophrenia: implementation status and attitude toward an upcoming living guideline. *Eur Arch Psychiatry Clin Neurosci* 2023;273:1587-98. doi:10.1007/s00406-023-01568-z
187 Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry* 2012;13:318-78. doi:10.3109/15622975.2012.696143
188 Leucht S, Arango C, Fleischhacker WW, et al. CINP Schizophrenia Guideline, 2011. https://cinp.org/Guidelines
189 Ostuzzi G, Barbui C, Hanlon C, et al. Mapping the evidence on pharmacological interventions for non-affective psychosis in humanitarian non-specialised settings: a UNHCR clinical guidance. *BMC Med* 2017;15:197. doi:10.1186/s12916-017-0960-z
190 Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016;388:86-97. doi:10.1016/S0140-6736(15)01121-6
191 Sawa A, Yang K, Cascella NG. Paradigm shift on the concept of schizophrenia that matches with both academic and clinical needs. *Schizophr Res* 2022;242:123-5. doi:10.1016/j.schres.2021.12.022
192 Tandon R, Keshavan M, Nasrallah H. •Reinventing schizophrenia: Updating the construct•. Project update and next steps. *Schizophr Res* 2023;252:345-7. doi:10.1016/j.schres.2023.01.025
193 Haendel MA, Chute CG, Robinson PN. Classification, Ontology, and Precision Medicine. *N Engl J Med* 2018;379:1452-62. doi:10.1056/NEJMra1615014
194 Behrens MM, Ali SS, Dao DN, et al. Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. *Science* 2007;318:1645-7. doi:10.1126/science.1148045

195 Niwa M, Jaaro-Peled H, Tankou S, et al. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science* 2013;339:335-9. doi:10.1126/science.1226931
196 Yilmaz M, Yalcin E, Presumey J, et al. Overexpression of schizophrenia susceptibility factor human complement C4A promotes excessive synaptic loss and behavioral changes in mice. *Nat Neurosci* 2021;24:214-24. doi:10.1038/s41593-020-00763-8
197 Popoli M, Yan Z, McEwen BS, et al. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci* 2011;13:22-37. doi:10.1038/nrn3138
198 Monin A, Baumann PS, Griffa A, et al. Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients. *Mol Psychiatry* 2015;20:827-38. doi:10.1038/mp.2014.88
199 Ajoy R, Lo YC, Ho MH, et al. CCL5 promotion of bioenergy metabolism is crucial for hippocampal synapse complex and memory formation. *Mol Psychiatry* 2021;26:6451-68. doi:10.1038/s41380-021-01103-3
200 Cuenod M, Steullet P, Cabungcal JH, et al. Caught in vicious circles: a perspective on dynamic feed-forward loops driving oxidative stress in schizophrenia. *Mol Psychiatry* 2022;27:1886-97. doi:10.1038/s41380-021-01374-w