REVIEW ARTICLE

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Schizophrenia

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Schizophrenia is a psychiatric syndrome characterized by psychotic symptoms of hallucinations, delusions, and disorganized speech, by negative symptoms such as decreased motivation and diminished expressiveness, and by cognitive deficits involving impaired executive functions, memory, and speed of mental processing. Schizophrenia affects nearly 1% of the world population and is among the top 10 global causes of disability.[1] However, there is wide variation in the ability of persons with schizophrenia to function in their daily lives, with some being severely disabled and others able to function at a high level.

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Initial Manifestations of Schizophrenia

The first indications of schizophrenia typically appear in the late teens and early twenties, but some children in whom schizophrenia later develops have social awkwardness, physical clumsiness, and lower intelligence quotients than their siblings at similar ages. Before the onset of psychosis, there is often a period of months or years that is characterized by subtle changes in behavior and declining function; this period is referred to as the psychosis prodrome. A typical example is a high-school or college student who becomes socially isolated, acquires odd beliefs or has perceptual anomalies such as hearing murmuring voices, and has deteriorating academic performance. The person or family typically seeks medical attention when the person begins to report hearing voices or has convictions about delusional beliefs.

Neurobiologic and Genetic Factors

On the basis of twin and family studies, heritable factors are estimated to explain 80% of the risk of schizophrenia in a population. However, only a small portion of this heritable component has been shown to be attributable to common disease-associated single-nucleotide variants, each with a small effect on risk,[2] or to larger but rare mutations, each with a putatively greater influence on risk.[3] Many of the genes that are identified in genomewide association and gene-expression profiling studies implicate pathways associated with the immune system, cytoskeletal development, and synaptic plasticity and function.[4,5] Environmental factors, including obstetrical complications, early-life adversity, and childhood residence in urban areas, putatively interact with genetic risks to influence liability to schizophrenia.[5]

Persons with schizophrenia have lower gray-matter volumes on magnetic resonance imaging than age-matched controls and fewer dendrites and dendritic spines in postmortem studies.[4,6,7] Among persons in the prodromal phase of psychosis, there is a greater rate of gray-matter loss over time in the prefrontal and parahippocampal regions than among persons in whom psychosis does not

develop. The rate of gray-matter loss has been associated with elevated levels of immunologic markers, such as tumor necrosis factor α, that participate in activation of brain microglia, which suggests that cytokine-mediated activation of microglia may play a role in the disorder.[8] This is supported by evidence that a mouse model of a human variant of the gene encoding complement C4, which is overrepresented in schizophrenia, causes increased synaptic pruning in mice.[9] These structural features are hypothesized to contribute to altered physiological activity and functional connectivity among the prefrontal cortex, temporal cortex, thalamus, hippocampus, and cerebellum.[10]

A currently prominent neurochemical model of schizophrenia came from the serendipitous observation that drugs that block dopamine receptors, particularly the D2 receptor, have antipsychotic properties.[11] It has been assumed that the efficacy of these drugs is due to D2 antagonism and that increased dopamine activity is in some manner involved in the pathophysiology of schizophrenia. Dopamine plays a role in what has been termed "reward-based learning," meaning that dopamine release is associated with the initiation of behaviors that predict a subsequent reward.[12] Increased dopamine synthesis has been observed in both the prodromal phase and the first-episode psychosis of schizophrenia, particularly in corticostriatal systems that are involved in evaluating the likelihood that on the basis of previous experience, a stimulus is salient to a reward.[13] If increased dopamine synthesis and release occur, as they are theorized to in schizophrenia, independent of previous experiences, there is a heightened sense of salience of otherwise innocuous stimuli, which could explain paranoia and ideas of reference that are dissociated from reality.[14]

This relatively simple theory that psychosis is related to excessive dopamine activity has been challenged by clinical observations as well as findings on the functioning of information processing in the prefrontal cortex.[11] There is a lag of 2 to 4 weeks between the peak blockade of D2 receptors by medications and clinical response, which suggests that the antipsychotic efficacy of these drugs may depend on other neurochemical mechanisms that arise as adaptations to sustained D2 receptor blockade rather than to decreased dopamine transmission. In addition, dopamine interacts with glutamate and γ-aminobutyric acid (GABA) in modulating the functioning of excitatory and inhibitory interneurons in cortical circuits. Postmortem studies suggest that there are alterations in the microstructure and functioning of these microcircuits in schizophrenia. These observations have led investigators to consider targeting glutamate and GABA signaling.[15]

Criteria for Schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5).

The specific DSM-5 criteria for schizophrenia are as follows:

The presence of at least two of the following five items, each present for a clinically significant portion of time during a 1-month period (or less if successfully treated), with at least one of them being items 1, 2, or 3: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (e.g., decreased motivation and diminished expressiveness).

For a clinically significant portion of the time since the onset of the disturbance, the level of functioning in one or more major areas (e.g., work, interpersonal relations, or self-care) is markedly below the level achieved before onset; when the onset is in childhood or adolescence, the expected level of interpersonal, academic, or occupational functioning is not achieved.

Continuous signs of the disturbance persist for a period of at least 6 months, which must include at least 1 month of symptoms (or less if successfully treated); prodromal symptoms often precede the active phase, and residual symptoms may follow it, characterized by mild or subthreshold forms of hallucinations or delusions.

Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms or any mood episodes that have occurred during active-phase symptoms have been present for a minority of the total duration of the active and residual periods of the illness.

The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse or a medication) or another medical condition.

If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms or schizophrenia, are also present for at least 1 month (or less if successfully treated).

In addition to the symptom domain areas identified in the first diagnostic criterion, assessment of cognition, depression, and mania symptom domains is vital for distinguishing between schizophrenia and other psychotic disorders.

EVALUATION FOR SCHIZOPHRENIA

The diagnosis of schizophrenia requires confirmation that patients meet established criteria for the disorder (see text box)[16] and ruling out of psychotic states that mimic the disorder. Patients are typically asked specific questions about common psychotic experiences such as hearing voices, thought broadcasting, and the sense of

Table 1. Commonly Prescribed Antipsychotic Medications.*

Medication	Usual Daily Dose	Formulations	Common Side Effects†	Notes
	mg			
Haloperidol‡	2–20	Oral, IM, LAI	EPS, elevated prolactin levels	
Perphenazine‡	12–24	Oral	EPS, elevated prolactin levels	
Clozapine	150–600	Oral	Sedation, metabolic effects, hypotension	Monitor for agranulocytosis; seizure risk
Risperidone	2–6	Oral, IM, LAI	EPS, elevated prolactin levels	
Olanzapine	10–20	Oral, IM, LAI	Metabolic effects	Restrictions for LAI
Quetiapine	150–800	Oral, oral ER tablet	Sedation, metabolic effects	
Ziprasidone	40–160	Oral, IM	Restlessness	Improved bioavailability when taken with food
Aripiprazole	10–15	Oral, IM, LAI	Restlessness	
Paliperidone	6–12	Oral ER tablet, LAI	EPS, elevated prolactin levels	
Iloperidone	12–24	Oral	Hypotension	
Asenapine	10–20	Sublingual tablet	Restlessness, elevated prolactin levels	
Lurasidone	40–80	Oral	Restlessness	Improved bioavailability when taken with food
Cariprazine	1.5–6	Oral	Restlessness	
Brexpiprazole	2–4	Oral	Restlessness	

* EPS denotes extrapyramidal side effects, ER extended release, IM intramuscular, and LAI long-acting injectable.
† Metabolic side effects include weight gain and insulin resistance.
‡ Haloperidol and perphenazine are first-generation antipsychotic drugs. The others are second-generation drugs.

being followed or watched by others. In parallel, questions can be directed at determining whether there are thoughts of harming themselves or harming others. An assessment of dangerousness, either to oneself or others, includes inquiring about hallucinations that command the patient to engage in dangerous or violent behavior, a history of such behavior, access to weapons, and the use of illicit drugs, especially stimulants. Informants who have had substantial contact with the patient can be essential for evaluating changes in the patient's behavior.

TREATMENT OF ACUTE SCHIZOPHRENIC PSYCHOSIS

Antipsychotic medications are effective for reducing psychotic symptoms in acute episodes of schizophrenia. In most circumstances, initiation of medication can occur after the history taking, physical examination, and basic laboratory evaluation. In patients who are agitated or uncooperative or who appear to be suffering, it may be safe to begin medications immediately after evaluation of vital signs. The selection of medication should be based on a person's past response to medication, the side effects that might be particularly harmful in individual circumstances, and routes of administration. Antipsychotic medications are most often administered orally, but several (Table 1) can be administered in a short-acting intramuscular formulation for patients who decline oral medication or for those who are agitated and for whom there is urgency in achieving a clinical response. Except for clozapine, most of the currently used antipsychotic medications have similar efficacy; however, they differ in side effects (Table 1).

Antipsychotic medications are effective when the levels in the central nervous system are sufficient to occupy approximately 70% of D2 receptors.[17] The doses that correspond to these levels are usually in the middle of the recommended range for each drug. Exceptions are

clozapine and quetiapine, which have lower receptor occupancies at drug doses that are clinically effective.[18] There is no evidence that increasing doses of an antipsychotic medication to achieve receptor occupancies above these levels will lead to increased efficacy, but higher doses increase the risk of adverse effects.

Treatment should generally occur in an environment that patients perceive as safe. During the initial days of drug treatment, it is advisable that dose adjustments be made to minimize side effects. Because there is a lag between achieving sufficient receptor occupancy and demonstrable antipsychotic effect, increasing the dose of oral medication in the first few days or weeks is unlikely to be helpful; however, acute agitation usually improves within the hours after the patient has received an intramuscular or oral dose. Improvement of a broader range of psychotic symptoms usually occurs during the first 2 weeks after the initiation of drug treatment.

Patients who have a first episode of schizophrenia tend to have a higher likelihood of response to antipsychotic medications, and often have a response to lower doses, than patients who have had multiple episodes.[19,20] They are also more vulnerable to the side effects of antipsychotic medications, including weight gain, sexual side effects, and extrapyramidal effects. Because the first experience with taking an antipsychotic medication may have an effect on a person's attitude toward drug treatment and later adherence, it is helpful to monitor and respond to early side effects.

MANAGEMENT OF A POOR OR PARTIAL RESPONSE

Persons with schizophrenia vary widely in their clinical response to an antipsychotic medication. Between 10 and 30% will have limited benefit; a larger percentage — at least 30% in some studies — show improvement but will have persistent psychotic or residual symptoms that affect their functioning and their quality of life.[21] Before concluding that a patient is not having a response to a medication, clinicians should consider possible causes of a partial response, including poor medication adherence, drug–drug interactions, and substance use. Several approaches have been studied for treating medication-resistant psychosis, including prescribing doses of antipsychotic medications that are higher than those usually recommended, adding a mood stabilizer (e.g., lithium or valproate), and adding a second antipsychotic medication. These strategies are used but are not well supported by empirical evidence.[19] In addition, these strategies can lead to adverse drug effects and can delay initiation of a trial of clozapine.

The most effective antipsychotic medication for patients with a poor or partial response is clozapine.[22,23] When clozapine first became available in the United States, it was reserved for severely ill patients who had been institutionalized on a long-term basis. Subsequently, trials have shown that it is also effective for patients with persistent psychotic symptoms who are living in the community[24] and whose symptoms interfere with their quality of life. Treatment with clozapine is generally undertaken for 8 to 12 weeks at a total daily dose of 150 to 600 mg. Measuring plasma concentrations of clozapine can be helpful if patients do not have a response or if they are having side effects. A response is more likely if the level of clozapine approximately 12 hours after an evening dose is above 350 ng per milliliter.[25]

Potentially fatal agranulocytosis develops in approximately 1% of patients who begin taking clozapine.[26] A total of 50 to 75% of cases of agranulocytosis occur during the first 18 weeks of treatment, and 85 to 90% occur during the first year. Monitoring the white-cell count and absolute neutrophil count and stopping clozapine when there is evidence of severe neutropenia or agranulocytosis have been effective for reducing the risk of subsequent complications. In the United States, patients who receive clozapine are required to be enrolled in a registry (www.clozapinerems.com) that records the white-cell count and absolute neutrophil count and attempts to ensure that prescriptions are not filled for patients whose counts are below thresholds in guidelines. Treatment with clozapine is recommended to be interrupted when the absolute neutrophil count is 500 to 999 per microliter, and it can be restarted when levels are 1000 per microliter or higher. Clozapine is discontinued if the absolute neutrophil count is below 500 per microliter.

Cognitive behavioral therapy (CBT) may be

effective for reducing persistent psychotic symptoms in patients who have a partial response to clozapine or other antipsychotic medications. Meta-analyses have indicated that the effect size of CBT as compared with control conditions is small to medium for psychotic symptoms and larger for the patient's report of distress related to these symptoms.[27] This approach is most effective for patients who have some preserved insight and are willing to explore the lack of a basis in reality of their specific symptoms.[28] For example, if a patient has the belief that people who are looking at him in a café are foreign government agents, the therapist may help the patient to consider alternative explanations for the glances of the café patrons. CBT is considered to be an evidence-based practice[29] and is recommended in guidelines for patients who have persistent psychotic symptoms and have preserved insight.

ANTIPSYCHOTIC MEDICATIONS FOR RELAPSE PREVENTION

The continued administration of antipsychotic medications after recovery from a psychotic episode has been shown to be effective in reducing the risk of a relapse of psychosis. In randomized trials comparing medication continuation with discontinuation, approximately 64% of patients have a relapse during the first year while receiving a placebo, as compared with 27% who have a relapse while receiving an antipsychotic medication.[30] Current practice is to continue antipsychotic medications indefinitely, even if the patient's condition has been stable for years or decades. However, many patients are reluctant to continue medication when their condition has become stable, particularly those who have had only a single episode or who have had unpleasant medication side effects. As a result, nonadherence to antipsychotic medications is the most common cause of psychotic relapse.[31]

Long-acting injectable antipsychotic medications can be prescribed when there is a concern about nonadherence. These drugs are administered as intramuscular injections every 2 to 12 weeks (depending on the formulation), which results in a relatively stable plasma concentration. For example, haloperidol decanoate is usually effective in the range of 50 to 200 mg every month, and paliperidone palmitate is usually effective at a dose of 78 to 234 mg monthly. Studies that have compared oral and long-acting antipsychotic medications (in patients having a first psychotic episode or those with multiple episodes of psychosis) have yielded mixed results, with a tendency for a lower incidence of relapse with long-acting agents.[32,33]

Although the condition of an individual patient who has recovered from an episode of psychosis may remain stable without long-term treatment, there are no methods for identifying these patients with a good prognosis, who represent 4 to 30% of patients who have recovered from a psychotic episode.[34] The observations that approximately one fourth of patients who have a response to antipsychotic drugs will have a relapse while receiving medication and that approximately three fourths of patients who have an initial response but who become nonadherent will have a relapse suggest that antipsychotic drugs are palliative rather than curative of the underlying vulnerability to psychotic symptoms.

CANNABIS AND SCHIZOPHRENIA

Past or current use of cannabis is common in persons with schizophrenia, particularly in young persons with a first episode. Use of cannabis has the potential for worsening psychotic symptoms and increasing apathy.[35] In addition, there is evidence that the use of cannabis is associated with an earlier onset of schizophrenia.[36] This may be the result of genetic risk factors that make persons vulnerable to the effects of cannabis.[37] Although a causal role of cannabis in psychosis has not been established, the association suggests that clinicians should discourage cannabis use in younger patients who are at risk for schizophrenia. Once schizophrenia has developed, patients should be advised that use of marijuana or synthetic cannabinoids has the potential to worsen the course of the illness and to provoke violence and suicidality.[38]

IMPROVING FUNCTIONING

Remission from psychosis is an important goal of treatment. However, many patients are also interested in improving functioning in areas such as work, education, independent living, and

Table 2. Evidence-Based Psychosocial Interventions for Schizophrenia.

Intervention	Population	Targeted Outcome
Assertive community treatment[40]	Persons with a history of repeated hospitalizations or recent homelessness	Reduced hospitalizations and homelessness
Supported employment[41]	Persons with a goal of employment	Employment
Skills training[42]	Persons with deficits in skills needed for everyday living	Improved living skills
Cognitive behavioral therapy[43]	Persons with persistent psychotic symptoms during antipsychotic treatment	Reduced psychotic symptoms
Family-based services[39]	Persons who have ongoing contact with family members	Reduced symptoms, improved treatment adherence, improved functioning
Psychosocial interventions for alcohol and substance use[44]	Persons with concurrent alcohol or drug use	Reduced substance use, reduced symptoms, improved functioning
Psychosocial interventions for weight management[45]	Persons who are overweight or obese	Weight loss

social relationships. Nonpharmacologic interventions, including social-skills training, supported employment, assertive community treatment, CBT, and family-based services, have been shown to be effective for improving outcomes in patients with schizophrenia.[39] These interventions (Table 2) may be indicated for different types of patients, and they are most effective for patients whose condition has first been stabilized with an antipsychotic medication.

SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

Managing the care of patients who are taking antipsychotic medications requires attention to side effects. Patients with schizophrenia may report side effects poorly, particularly side effects that are subjective, such as restlessness, stiffness, or sedation. It is recommended that treating clinicians adhere to a strategy for monitoring side effects (as outlined in Table 3) that is derived from consensus recommendations.[46,47]

ACUTE EXTRAPYRAMIDAL SIDE EFFECTS

The effectiveness of antipsychotic medications is related to their antagonist activity at dopamine receptors in the mesolimbic dopamine tract,[11] but their parallel activity in reducing dopamine activity in nigrostriatal pathways leads to extrapyramidal side effects. Akathisia is the most common of these features. It is characterized by restless movements — usually restless leg movements — as well as the subjective unpleasant experience of restlessness. Drug-induced parkinsonism can also cause any of the symptoms of idiopathic parkinsonism, including tremor, rigidity, dystonia, impaired gait, and psychomotor retardation. Mild extrapyramidal syndromes can be detected by observation of a decreased arm swing while the patient walks. Drug-induced dystonias are characterized by involuntary muscle contractions that bring body parts into a contorted position, usually in the neck, jaw, or arms.

Acute extrapyramidal side effects are typically managed by reducing the dose of the antipsychotic medication, changing to an antipsychotic medication that is putatively associated with less of these effects, or adding anticholinergic medications (e.g., benztropine), which are usually effective for acute extrapyramidal symptoms but may produce side effects including dry mouth, blurred vision, and constipation. Benzodiazepines or beta-blockers (e.g., propranolol) may also be effective but are not as widely prescribed.

TARDIVE DYSKINESIA

Tardive dyskinesias are abnormal movements that emerge after months or years of treatment with an antipsychotic medication. The movements are usually slow and athetoid or rapid choreiform jerks; both types of movements commonly manifest in the mouth, face, jaw, tongue, hands, or feet. Older patients and those with a history of acute extrapyramidal symptoms are at higher risk for tardive dyskinesia. A review of 12 trials[48]

Table 3. Guidelines for Monitoring Side Effects of Antipsychotic Medications.*

Evaluation	When to Evaluate
Acute extrapyramidal side effects	Every visit until dose stabilized; every visit after dose increase
Tardive dyskinesia	Every 6–12 mo; every 6 mo for drugs with a high risk of extrapyramidal side effects; every 3 mo for older patients receiving drugs with a high risk of such effects
Body weight, blood pressure, and heart rate	Every visit for 6 mo after initiation of a new antipsychotic medication; quarterly if condition is stable
Fasting glucose level or glycated hemoglobin level	Before initiation of a new antipsychotic medication, at 12 wk, and then annually
Lipid panel	Before initiation of a new antipsychotic medication, at 12 wk, and then annually

* Derived from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.[16]

showed that the annualized incidence of tardive dyskinesia was 3.9% with second-generation antipsychotic drugs, such as risperidone and quetiapine, and 5.5% with first-generation drugs, such as haloperidol, perphenazine, and chlorpromazine. The prevalence of tardive dyskinesia among adults in these trials was 13% with second-generation antipsychotic drugs and 32% with first-generation drugs.

There is some evidence that tardive dyskinesia is related to alterations in D2 receptors. A strategy for managing tardive dyskinesia is to lower the dose of the antipsychotic drug or to change to quetiapine or clozapine, which are associated with a lower risk of tardive symptoms than other antipsychotic drugs.[49] Drugs based on tetrabenazine that inhibit vesicular monoamine transporter 2 may also be effective for treating tardive dyskinesia.[50]

METABOLIC SIDE EFFECTS

Metabolic side effects of antipsychotic medications include weight gain, elevations in lipid levels, and insulin resistance, all of which increase the risk of cardiovascular disease. The magnitude of the metabolic changes that are related to an antipsychotic medication can be large, particularly in younger patients. It has been recommended that patients with schizophrenia receive regular monitoring of weight and glucose and lipid levels[46,47] (Table 3). If changes in these measures are temporally related to the initiation of an antipsychotic medication, changing to a drug that is not associated with these effects (e.g., lurasidone or ziprasidone) can be helpful. Nonpharmacologic interventions that support lifestyle changes such as improved diet and exercise have also been shown in controlled trials to reduce these metabolic changes.[29] If changing the antipsychotic drug is not possible and lifestyle interventions are not effective, adding metformin to the patient's medications can be helpful in reducing the biochemical effects of the metabolic syndrome.[51]

Antipsychotic medications — particularly first-generation antipsychotic drugs and the second-generation drugs risperidone, paliperidone, and asenapine — can elevate prolactin levels. The elevations can result in galactorrhea and menstrual disturbances in women and sexual dysfunction and gynecomastia in men. The sexual side effects can be disturbing and are a common cause of medication nonadherence. Other common side effects of antipsychotic medications that have received less attention include sedation, orthostatic hypotension, and anticholinergic effects.

CONCLUSIONS

Most persons with schizophrenia benefit from combined antipsychotic medication and nonpharmacologic treatments that address their personal goals. Principles of drug treatment include prescribing the lowest effective dose of an antipsychotic medication, monitoring and addressing side effects, and prescribing clozapine if patients continue to have symptoms of psychosis. Several promising approaches for improving outcomes in schizophrenia are under study, in-

cluding drugs targeting the glutamate–*N*-methyl-D-aspartate (NMDA) cascade that may help mitigate persistent psychotic symptoms, negative symptoms, and cognitive deficits in patients with established illness. Attention is being focused on the early administration of psychosocial interventions to reduce persistent disability.

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