# New Hope in Pharmacotherapy for Schizophrenia

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Schizophrenia is a debilitating mental disorder that, in the US, has a lifetime prevalence of approximately 1%.[1] It has been estimated that approximately 0.025% to 0.05% of the total population is treated for schizophrenia in any 1 year. The illness represents a significant economic and social burden. Since the 1950s, the disorder has been treated with antipsychotic drugs; these therapeutic agents primarily have antidopaminergic activity. However, treatment with typical or first-generation antipsychotic drugs, which alleviate many of the so-called positive symptoms of schizophrenia (eg, delusions, hallucinations), has been associated with the development of extrapyramidal symptoms, which may account for the high incidence of noncompliance. Many patients with schizophrenia find the first-generation antipsychotic medications ineffective or only partially beneficial. The second-generation antipsychotic agents, which target the serotonin signaling pathway in addition to the dopamine system, alleviate not only positive symptoms of schizophrenia but also negative symptoms (eg, flat affect, poverty of speech) and have provided significant benefits over the first-generation drugs. This article reviews the efficacy and safety of the second generation of antipsychotic agents and highlights the importance of investing in effective medication.

CLINICAL CHARACTERISTICS

Schizophrenia is usually a chronic, lifelong illness with a peak age of onset in the mid-20s. In 1988, the US National Advisory Mental Health Council stated that "in schizophrenia the entire human personality is laid waste and the psychological and social building blocks of everyday life are crushed, often beyond recognition."[2] Factors that may increase the risk for developing schizophrenia include family history, perinatal complications, chemical stress, or stressful life events.[3]
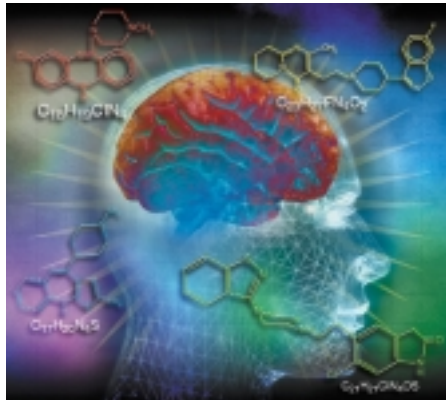
Typically, affected persons enter into a prodromal phase, characterized by features such as social withdrawal, perceptual disturbances, mood changes, and academic and occupational deterioration. The illness progresses toward the development of positive symptoms, such as delusions and hallucinations. Relatively few patients experience one or several episodes with no lasting impairment; the majority of patients (52%) experience multiple episodes against a background of gradual deterioration.[3] Chronic schizophrenia is associated with a deficit syndrome in which the affected person becomes withdrawn, uncommunicative, and asocial.

A psychiatrist can help a patient and family members to identify early signs and symptoms of acute episodes of schizophrenia. Such early identification can allow the patient to gain a feeling of mastery over the illness and can ensure that adequate treatment is initiated as early as possible in the course of the disease.

A 10-year study evaluated mortality rates among 891 patients with schizophrenia who were admitted to a hospital for treatment[4]; if a patient was admitted more than once, only the last admission was evaluated. Adjusting for age and sex, the overall mortality among patients with schizophrenia was shown to be twice that of the general population, with suicide being the main cause of death. Overall, approximately 50% of persons with schizophrenia attempt suicide and 10% ultimately succeed—usually less than 2 years after discharge from the hospital.[4] There is no clear explanation as to why the risk for mortality is more pronounced during the first 2 years after hospital discharge, but it is possibly

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attributable to the severity of the illness early in its course.

A substantial number of chronically ill patients with schizophrenia are discharged to their families, and caring for them creates a tremendous emotional and economic burden. Frequently, the psychosocial effects of the disorder result in many patients having emotional, familial, academic, occupational, and financial issues for which they require assistance. Practical problems often result from unemployment, lack of a social life, and difficulties with self-care.[5] Additional stress occurs when health care professionals do not provide relevant information on the disorder and its treatment. The problems that patients with schizophrenia experience have been linked to an increased risk of alcohol and drug abuse and homelessness.[6]

ETIOLOGY AND PATHOPHYSIOLOGY

Although the severity of schizophrenia has been recognized for many years, its etiology and pathophysiology are not fully understood. It is has been hypothesized that the positive and negative symptoms of schizophrenia are partly the result of hyperdopaminergic activity in the mesolimbic system, which is 1 of the 3 main systems that comprise the dopaminergic pathways. The other 2 principal systems are the nigrostriatal and the mesocortical systems; each system name is indicative of the site of origin and output of dopamine.

Patients with schizophrenia characteristically exhibit cognitive deficits indicative of damage to forebrain areas, such as the dorsolateral prefrontal cortex, where fibers from the cell bodies of the mesolimbic and mesocortical systems terminate.[7] The hyperdopaminergic hypothesis has been supported by the finding that patients with schizophrenia release more dopamine at the synaptic junction in response to amphetamine stimulation than do patients without schizophrenia. This increase in dopamine release has been associated with a worsening of positive symptoms.[8,9]

TREATMENT

The development and implementation of a treatment regimen for a patient with schizophrenia requires the consideration of many issues, including the current clinical status of the patient, family history of mental illness, and disease duration. It is important to consider the available therapeutic options in terms of their clinical effectiveness and effects on a patient's quality of life.

Antipsychotic drugs are a critical component in the management of patients with schizophrenia and are used to treat acute episodes, prevent future episodes, and improve residual symptoms of the disorder, such as

impaired cognitive functioning, alogia, and avolition, as well as continuing negative symptoms. (Some negative symptoms may continue in the absence of a complete set of active symptoms after treatment.) Maintenance treatment with antipsychotic medications is usually continued with oral or depot formulations for at least 1 year after the first episode. Approximately 75% of patients will relapse within 12 to 18 months of the discontinuation of treatment.[10,11]

First-Generation (Typical) Antipsychotics

Phenothiazines, the first effective antipsychotic drugs, have been available since the 1950s. Their antipsychotic effect is manifested in 2 ways: (1) through control of agitation and aggression (occurring within a few minutes or a few hours of treatment) and (2) through alleviation of psychotic symptoms (occurring after days or weeks of treatment).

The biochemical properties of chlorpromazine, a phenothiazine, were first described in the early 1950s. It was proposed that the blockade of dopamine receptors by chlorpromazine resulted in dopamine depletion and accounted for its antipsychotic activity. The 2000 Nobel Prize in medicine was awarded in part to Arvid Carlsson for the description of the dopamine receptor–antagonistic mode of action of antipsychotic drugs.[12] This mechanism gave support to the hyperdopaminergic hypothesis of schizophrenia and was used as the basis for development of other antipsychotic drugs. To date, the principal aim of pharmacologic therapy for schizophrenia has been to alleviate hyperdopaminergia in the mesolimbic and mesocortical systems.

The dopamine receptors (*see* Table 1) are categorized as follows: D_1, D_2, D_3, D_4, D_5, D_1-like, and D_2-like. The receptors are distinguished on the basis of whether they stimulate adenylyl cyclase as a second messenger.[13] The D_2 dopamine receptors are pharmacologically more important than the other receptors in the central nervous system and have thus been the principal targets. It is thought that dopamine-receptor blockade in the mesolimbic and mesocortical systems is responsible for the antipsychotic efficacy of the medications.

Chlorpromazine and other first-generation antipsychotic agents have primarily antidopaminergic activity. These compounds alleviate and prevent the recurrence of the positive symptoms of schizophrenia.[14] However, blockade of dopamine receptors in the nigrostriatal system by first-generation antipsychotic agents causes extrapyramidal symptoms in approximately 75% of patients.[14,15] The development of adverse effects such as akathisia, dystonia, parkinsonism, and eventually tardive

dyskinesia is a major cause of noncompliance after treatment with this group of antipsychotics.[16] Severe adverse effects such as tardive dyskinesia are among the major factors leading to noncompliance.[17] It has been estimated that noncompliance with first-generation antipsychotics may occur in approximately 48% of patients in the first year of treatment and 74% of patients in the second year.[18] Many patients with schizophrenia (30%–60%) find typical antipsychotic agents ineffective or only partially beneficial.[3] However, this may be partly attributable to the limited action of first-generation antipsychotic agents on negative and cognitive symptoms.[3]

Unfortunately, drugs prescribed to counter extrapyramidal symptoms, such as benztropine and procyclidine, have their own spectra of adverse events (eg, dry mouth, dizziness, blurred vision, sedation, and cognition deficits such as confusion). Furthermore, muscarinic receptor–antagonistic medications, such as procyclidine and benztropine, which are used routinely to treat extrapyramidal symptoms, have become substances of abuse.[19]

Second-Generation (Atypical) Antipsychotics

Although the dopamine receptors, especially D_2, have been the principal targets of pharmacologic agents in the treatment of schizophrenia, it is becoming clearer that pharmacologic treatment can be improved by targeting other receptor types. Patients with schizophrenia who experienced parkinsonism and/or akathisia during treatment with typical antipsychotics showed higher D_2 occupancies (76%–89% versus 70%–81%) than did those who remained free of such adverse effects.[20]

The serotoninergic system is potentially an important target for pharmacologic agents. Interestingly, not only are first-generation antipsychotics potent antagonists at D_2 receptors, but they also have varying serotoninergic interactions ranging from negligible (eg, with haloperidol) to moderate (eg, with chlorpromazine).

The distribution of neurons containing serotonin is widespread and is similar to that of noradrenergic neurons. The cells occur in several large clusters in the pons and upper medulla, which lie close to the midline, and are often referred to as *raphe nuclei*. Those cells situated rostrally project to many parts of the cortex, hippocampus, basal ganglia, limbic system, and hypothalamus. The caudally situated cells project to the cerebellum, medulla, and spinal cord.[21] The main subtypes of serotonin receptors are shown in **Table 1**. Most of the functional information available on serotonin receptors relates to the following types—5-HT_1, 5-HT_2, and

Table 1. Roles of Dopamine and Serotonin Receptors

Receptor	Function
Dopamine	
D_1	Emotion, stereotypic behavior, motor control, mood
D_2	Emotion, stereotypic behavior, motor control, endocrine control, arousal, mood
D_3	Emotion, stereotypic behavior, motor control
D_4	Emotion, stereotypic behavior, motor control
D_5	Motor control, autonomic and endocrine control
Serotonin	
5-HT_{1A}	Sleep, feeding, thermoregulation, anxiety
5-HT_{1B}	Presynaptic inhibition
5-HT_{1D}	Cerebral vasoconstriction, locomotion
5-HT_{2A}	Neuronal excitation
5-HT_{2B}	Not known
5-HT_{2C}	Cerebral spinal fluid secretion
5-HT_3	Neuronal excitation, anxiety
5-HT_4	Neuronal excitation
5-HT_5	Not known
5-HT_6	Not known
5-HT_7	Not known

5-HT = serotonin.

Data from Rang et al,[21] Rang et al,[22] Seeman,[23] and Sibley and Monsma.[24]

5-HT_3. All serotonin receptors are G-protein–coupled receptors, except for 5-HT_3, which is a ligand-gated cation channel, and all are expressed in the central nervous system.

Recently developed second-generation (or atypical) antipsychotic agents have chemical structures and pharmacologic profiles dissimilar to those of first-generation antipsychotic agents. They have in common with each other a higher affinity for serotonin receptors than for dopamine receptors. Five second-generation antipsychotic agents now exist: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone.

The term *atypical antipsychotic agent* was first applied to clozapine, which, in comparison to typical antipsychotic agents, produces substantially fewer extrapyramidal symptoms at therapeutic doses. Risperidone, olanzapine, quetiapine, and ziprasidone are also better tolerated

Table 2. Features of Major Antipsychotic Medications

Drug	Efficacy	Generation of EPS	Other features
Chlorpromazine	Benchmark treatment for persons with psychoses	Some	Some anticholinergic activity; sedation a common adverse effect
Clozapine	Associated with lower risk of relapse than are typical antipsychotics; more frequent clinically important improvements than with typical antipsychotics*	Rare	Sedation common, weight gain, risk of agranulocytosis
Risperidone	Higher proportion of patients showing clinical improvement than with typical antipsychotics[†]	Rare	Little sedative effect; some weight gain and tachycardia, increased prolactin
Olanzapine	Significantly better improvement with dosages of 10 mg/day to 20 mg/day on Positive and Negative Symptom Scale (PANSS) than placebo	Rare	Weight gain
Quetiapine	Significant clinical improvements versus placebo, with excellent tolerability profile; at least as effective as haloperidol and chlorpromazine concerning positive symptoms and improved efficacy concerning negative symptoms[‡]; significantly higher patient response to quetiapine (Seroquel) than to haloperidol[‖]; superior response rate compared with haloperidol for partial responders[#]; equivalent to risperidone in efficacy[**]; appears to be at least as effective as olanzapine (Data on file with AstraZeneca, Wilmington, DE)	Placebo levels across the full dosage range[§]	Not associated with increases in prolactin across the full dosage range[§]; no association with weight changes across the dosage range; significantly better tolerability with respect to EPS than with chlorpromazine[¶] or haloperidol[‡]; significantly lower incidence of substantive EPS compared with risperidone (Data on file with AstraZeneca, Wilmington, DE)
Ziprasidone	More effective than placebo and equally effective as haloperidol with positive symptoms but increased efficacy with negative symptoms[††]	Less EPS than with haloperidol	Nausea and vomiting

EPS = extrapyramidal symptoms.

*Data from Essali et al.[27]

[†]Data from Song.[28]

[‡]Data from Copolov et al.[29]

[§]Data from Arvanitis and Miller.**[30]**

[‖]Data from Kasper and Muller-Spahn.[31]

[¶]Data from Peuskens and Link.[32]

[#]Data from Emsley et al.[33]

[**]Data from Mullen et al.[34]

[††]Data from Bagnall et al.[35]

than are the first-generation antipsychotic agents, and increase patient compliance because of improved subjectivity.[25] Second-generation antipsychotic agents target both positive and negative symptoms of schizophrenia and have provided significant benefits over first-generation drugs in the treatment of the disorder.[26] Relevant clinical features of second-generation antipsychotic agents are described below and are summarized in **Table 2**.

Clozapine. Clozapine, the prototype of the second-generation antipsychotics, was introduced in Europe in 1966. It is the first of the serotonin receptor/dopamine receptor antagonists. Clozapine has a high affinity for a wide range of neurotransmitter binding sites. It was

distinguished from pre-existing antipsychotics by its high affinity for the $5\text{-}HT_{2A}$ receptor, the primary function of which is neuronal excitation (Table 1).[36] This binding profile accounts for the beneficial effects of clozapine on both the positive and negative symptoms of schizophrenia and also for the decreased incidence of extrapyramidal symptoms.[36] Clozapine is beneficial in treating at least 30% of patients previously described as treatment resistant.[36] Unfortunately, clozapine is highly toxic and causes agranulocytosis in 0.6% of patients, which has led to mandatory hematologic monitoring. Other common adverse effects include weight gain, sedation, sialorrhea, and an increased risk for seizures with dosages greater than 600 mg/day.[36,37]

Risperidone. Risperidone is a potent $5\text{-}HT_2$ receptor antagonist; at high doses, it also acts as a D_2 antagonist. A study by Chouinard and colleagues has shown that it is at least as effective in reducing the positive and more effective in reducing the negative symptoms of schizophrenia than is the first-generation antipsychotic drug haloperidol.[38] Risperidone is well tolerated at doses less than 10 mg daily; however, there may be increased risk for parkinsonism in patients who require higher doses.[38] The most frequently reported adverse effects are sedation, anxiety, headache, nausea, and weight gain, to some extent. Risperidone has also been shown to elevate prolactin levels, resulting in sexual dysfunction (eg, galactorrhea, menstrual disturbances, decreased libido, erectile dysfunction) in some patients.[39,40]

Olanzapine. Olanzapine is structurally similar to clozapine and displays a high affinity for a wide spectrum of neurotransmitter binding sites. It has been shown to improve positive and negative symptom efficacy and is associated with a low risk of tardive dyskinesia.[41] The recommended dosage range is 10 to 20 mg/day; however, because of its potential to result in orthostatic changes in blood pressure and an increase in parkinsonism and akathisia at dosages greater than 20 mg/day, a lower starting dosage (2.5 mg or 5 mg daily) should be considered for medication-sensitive populations. Other commonly reported adverse effects include sedation, dizziness, excessive appetite with weight gain, and anticholinergic effects.[42,43] In some patients, olanzapine treatment may cause transient asymptomatic hepatic transaminase level elevations and minor increases in prolactin levels.[42] Olanzapine treatment may be associated with insulin resistance and elevated levels of insulin, leptin, and blood lipids.[44]

Quetiapine. Like olanzapine, quetiapine is a clozapine analogue and consequently has a similar receptor binding profile. It is a potent $5\text{-}HT_{2A}$ receptor antago-

nist with weak D_2 effects.[30,45] The incidence of extrapyramidal symptoms is comparable to placebo across the entire dosage range and is lower than that of haloperidol[30] and chlorpromazine.[32] Quetiapine does not increase levels of prolactin and, therefore, may offer improved compliance compared with other antipsychotics.[45] Adverse effects associated with quetiapine include somnolence (which generally resolves with the continued administration of quetiapine) and orthostatic hypotension (which may occur during the initial dose titration period).[45,46] The dosage range for effectively targeting positive and negative symptoms is between 150 and 800 mg/day, with preliminary studies indicating that the most effective dosage may be 300 mg/day.[46]

Ziprasidone. Ziprasidone has a high affinity for $5\text{-}HT_2$ and D_2 receptors, and as with other second-generation antipsychotic agents, studies have shown it has a favorable antipsychotic action on both positive and negative symptoms.[47] Also, its side effect profile is quite favorable with respect to extrapyramidal symptoms and weight gain. It is available in the US; however, recent evidence of electrocardiographic changes has postponed its approval for launch by the Therapeutic Products Programme of Canada.[48]

COST ISSUES

Unfortunately, cost limits the availability of second-generation antipsychotic agents. Prices of first-generation antipsychotic agents are pennies per day as opposed to dollars per day for second-generation medications. It is believed, however, that short-term policies aimed at controlling expenditures relating to drugs do not take into account the social and long-term effect of mental illness. It is well established that schizophrenia is an expensive disease. A study in Australia found that schizophrenia costs 6 times more than heart disease per patient.[48] In 1990, schizophrenia accounted for 2.5% ($16–$19 billion) of the total US direct health care expenditures.[49] Indirect costs from factors such as loss of productivity have been estimated at $46 billion.[50] Most dollars are spent on hospitalization and long-term residential care and not on medication. Consequently, administration of effective treatment, despite the short-term relative increase in immediate cost, may ultimately reduce the economic burden of the disorder. This has been recognized by the Canadian Psychiatric Association, which has issued a position statement urging all publicly supported drug plan formularies in Canada to provide timely and unrestricted access to second-generation antipsychotic agents.[51]

CONCLUSION

Schizophrenia is a severe, debilitating, and costly illness. Although first-generation antipsychotic agents provide reasonable relief from symptoms for some patients, they have failed to offer persistent relief with regard to all the symptoms associated with the disorder. Most notably, they are ineffective when targeting negative, affective, and cognitive symptoms. Furthermore, the frequently intolerable, distressing, and potentially disfiguring adverse effects of these medications are among the most important factors leading to nonadherence, ultimately worsening the prognosis and outcome of patients.

The second generation of antipsychotic drugs treat more of the symptoms associated with schizophrenia than do the typical agents. Studies are currently underway to show clear improvement and protection against cognitive dysfunction. Although some second-generation antipsychotic agents cause adverse effects such as weight gain and sexual dysfunction, they have a more favorable side effect profile when compared with first-generation drugs. In particular, the incidence of extrapyramidal symptoms—a major cause of intolerability and noncompliance with first-generation medications—is reduced.[14,52] This benefit leads to a decreased risk for tardive dyskinesia, a potentially disfiguring and irreversible side effect.

There are several components to the comprehensive treatment of schizophrenia, including psychological and psychosocial therapy. Patients with schizophrenia often require an array of psychiatric, general medical, rehabilitative, and social services. The clear clinical improvement and increased tolerability after treatment with second-generation antipsychotic agents should enhance the benefit gained from psychosocial interventions (eg, cognitive remediation and rehabilitation). There is increasing optimism that as the treatment of schizophrenia improves, primary care practitioners will be more able and willing to participate in a shared-care model with psychiatrists. Pharmacists can also contribute to the management of drug therapy for schizophrenia; they are in an ideal position to assess the drug acceptability over a long period of time. Therefore, treatment of the disorder should now involve multidisciplinary intervention.

To date, none of the antipsychotic medications is completely effective, and undoubtedly, the theory of hyperdopaminergia as the sole root of schizophrenic-like symptoms is too simplistic. Recent evidence clearly points toward a heterogenous etiology. Attention has focused on the mesocortical system and on neuroreceptors and neurotransmitters such as norepinephrine, serotonin, and glutamate in the etiology of the disorder. More effective therapeutic approaches and novel drug targets are needed to improve the prognosis of patients. Nevertheless, the development of second-generation antipsychotic agents has created hope for patients with schizophrenia and their families, helping them to obtain a more positive outlook on life and the future. **HP**

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