

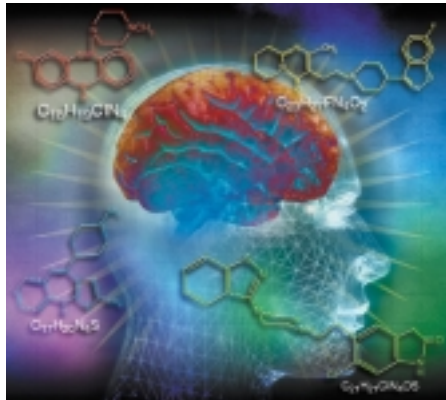
New Hope in Pharmacotherapy for Schizophrenia

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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 treatment⁴; 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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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 antipsy-

chotic 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

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distinguished from pre-existing antipsychotics by its high affinity for the 5-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-HT₂ receptor antagonist; at high doses, it also acts as a D₂ 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-HT_{2A} receptor antago-

nist with weak D₂ effects.^{30,45} The incidence of extrapyramidal symptoms is comparable to placebo across the entire dosage range and is lower than that of haloperidol³⁰ 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-HT₂ and D₂ 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 heterogeneous 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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REFERENCES

1. Jablensky A. Schizophrenia: the epidemiological horizon. In: Hirsch SR, Weinberger DR, editors. *Schizophrenia*. Oxford: Blackwell Science; 1995:212–5.
2. US National Advisory Mental Health Council, 1988.
3. Carpenter WT Jr, Buchanan RW. Schizophrenia. *N Engl J Med* 1994;330:681–90.
4. Black DW. Mortality in schizophrenia—the Iowa Record-Linkage Study: a comparison with general population mortality. *Psychosomatics* 1988;29:55–60.
5. Goldman HH. Mental illness and family burden: a public health perspective. *Hosp Community Psychiatry* 1982;33:557–60.
6. Attkisson C, Cook J, Karno M, et al. Clinical services research. *Schizophr Bull* 1992;18:561–626.
7. Lieh-Mak F, Lee PW. Cognitive deficit measures in schizophrenia: factor structure and clinical correlates. *Am J Psychiatry* 1997;154(6 Suppl):39–46.
8. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* 1998;155:761–7.
9. Breier A, Su TP, Saunders R, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA* 1997;94:2569–74.
10. Kane JM. Schizophrenia. *N Engl J Med* 1996;334:34–41.
11. Livingstone MG. Management of schizophrenia. *Prescribers J* 1996;36:206–15.
12. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol (Copenh)* 1963;20:140–4.
13. Keabian JW, Calne DB. Multiple receptors for dopamine. *Nature* 1979;277:93–6.
14. Ballus C. Effects of anti-psychotics on the clinical and psychosocial behavior of patients with schizophrenia. *Schizophr Res* 1997;28:247–55.
15. Niemegeers CJE, Janssen PAJ. A systematic study of the pharmacological activities of dopamine antagonists. *Life Sciences* 1978;24:2201–16.

16. Owens DG. Extrapyramidal side effects and tolerability of risperidone: a review. *J Clin Psychiatry* 1994;55:29–35.
17. Kemp R, Hayward P, Applewhaite G, et al. Compliance therapy in psychotic patients: randomised control trial. *BMJ* 1996;312:345–9.
18. Weiden P. International Congress of Schizophrenia, San Diego 1996 [abstract].
19. World Health Organization. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. *Br J Psychiatr* 1990;56:412.
20. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Arch Gen Psychiatry* 1992;49:538–44.
21. Rang HP, Dale MM, Ritter JM, Gardner P, editors. Other transmitters and modulators. *Pharmacology*. 4th ed. Edinburgh: Churchill Livingstone; 1999:486–90.
22. Rang HP, Dale MM, Ritter JM, Gardner P, editors. Other peripheral mediators: 5-hydroxytryptamine and purines. *Pharmacology*. 4th ed. Edinburgh: Churchill Livingstone; 1999:167.
23. Seeman P. Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. *Neuropsychopharmacology* 1992;7:261–84.
24. Sibley DR, Monsma FJ Jr. Molecular biology of dopamine receptors. *Trends Pharmacol Sci* 1992;13:61–9.
25. Voruganti L, Cortese L, Oyewumi L, et al. Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. *Schizophr Res* 2000;43:135–45.
26. Meltzer HY. Pre-clinical pharmacology of atypical antipsychotic drugs: A selective review. *Br J Psychiatr* 1996; 168(Suppl 29):23–31.
27. Essali MA, Rezk E, Wahlbeck K, et al. Clozapine versus 'typical' neuroleptic medication for schizophrenia. In: *Schizophrenia module of the Cochrane Database of Systemic Reviews*. Adams CE, de Jesus Mari J, White P, editors. The Cochrane Collaboration Issue 2. Oxford: Update Software; 1997.
28. Song F. Risperidone in the treatment of schizophrenia: a meta-analysis of randomized controlled trials. *J Psychopharmacol* 1997;11:65–71.
29. Copolov DL, Link CG, Kowalczyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, "Seroquel") and haloperidol in schizophrenia. *Psychol Med* 2000;30:95–105.
30. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatr* 1997;42:233–46.
31. Kasper S, Muller-Spahn F. Review of quetiapine and its clinical applications in schizophrenia. *Expert Opin Pharmacother* 2000;1:783–801.
32. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiar Scand* 1997;96:265–73.
33. Emsley RA, Raniwalla J, Bailey PJ, Jones AM. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. *Int Clin Psychopharmacol* 2000;15:121–31.
34. Mullen J, Reinstein M, Bari M, et al. Quetiapine and risperidone in outpatients with psychotic disorders: results of the QUEST trial. Presented at ECNP 1999, London, UK.
35. Bagnall A, Lewis, Leitner ML. Ziprasidone for schizophrenia and severe mental illness. *Cochrane Database Syst Rev* 2000;4:CD001945.
36. Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull* 1995;21:579–91.
37. Prescribing information of clozapine. Available at: <http://www.pharma.us.novartis.com>.
38. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; 13:25–40.
39. Prescribing information of risperidone. Available at: <http://www.risperdal.com>.
40. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. *Br J Psychiatr* 1995; 166:712–26; discussion 727–33.
41. Fulton B, Goa KL. Olanzapine: a review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drug* 1997; 53:281–98.
42. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schioaffective and shizophreniform disorders: results of an international collaborative trial. *Am J Psychiatr* 1997;154:457–65.
43. Prescribing information of olanzapine. Available at: <http://www.lilly.com>
44. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry* 2000;61:742–9.
45. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *J Clin Psychopharmacol* 1996;16:158–69.
46. Prescribing information of quetiapine. Available at: <http://www.astrazeneca-us.com>
47. Daniel DG, Zimbardo DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology* 1999;20:491–505.

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48. Andrews G, Hall W, Goldstein G, et al. The economic costs of schizophrenia. Implications for public policy. *Arch Gen Psychiatry* 1985;42:537–43.
49. Rupp A, Keith SJ. The costs of schizophrenia: assessing the burden. *Psychiatr Clin North Am* 1993;16:413–23.
50. Wyatt RJ, Hunter I, Leary MC, Taylor E. An economic evaluation of schizophrenia—1991. *Soc Psychiatry Psychiatr Epidemiol* 1995;30:196–205.
51. Canadian Psychiatric Association Position Statement on Access to New Medications. *Bulletin* 1998;30(4):insert.
52. Cortese L, Malla A, Harricharan R, et al. Movement disorders and clinical correlates in drug-naive patients with psychosis [Abstract]. *International Congress on Schizophrenia Research*; April 2001; Davos, Switzerland.

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