Similarities and Differences Among Antipsychotics

Carol A. Tamminga, M.D.

Most antipsychotic drugs act equivalently and potently on the symptoms of schizophrenia, with clozapine as the notable exception. Negative symptoms and cognitive deficits are strongly associated with poor prognosis; some reports suggest that these symptoms respond better to second- than to first-generation antipsychotics. Although second-generation antipsychotics exert their action through a blockade of dopamine and serotonin receptors (and some have a more complex action), each has a different set of pharmacologic characteristics, including side effects. Due to the differences among antipsychotics available today, optimizing treatment for individual patients requires choosing the most appropriate drug and, if necessary, switching to a different drug if the first proves unsatisfactory. The treating physician must carefully match the diverse needs of schizophrenic patients with the varied characteristics of the second-generation antipsychotics.

(J Clin Psychiatry 2003;64[suppl 17]:7–10)

Schizophrenia as an illness has long been recognized but remains even now without a defined pathophysiology. Whether schizophrenia is a single illness with multiple manifestations or several illnesses with a common symptom set is still unknown. From antiquity, psychosis has been ascribed to various causes ranging from demonic possession to poor mothering. Schizophrenia was first broadly defined as an illness near the end of the 19th century.

Mean age at onset of schizophrenia is late adolescence or early adulthood, after which the illness runs a chronic course, usually for the remainder of the person's life. Prognosis is poor. Researchers have categorized the heterogeneous symptoms of schizophrenia into 3 symptom clusters or domains: positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms include hallucinations, delusions, and reality distortions. Negative symptoms include anhedonia, alogia, and social withdrawal. Cognitive deficits include alterations of attention, working memory, and executive function. There are also neurophysiologic changes associated with schizophrenia. Few people with schizophrenia can conduct personal relationships or maintain regular employment. Although psychosis is the hallmark of schizophrenia, poor psychosocial function and poor overall outcome are largely associated with negative symptoms and cognitive deficits.

From the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas.

Presented at the symposium "The Case for Physician Choice: Implications for Restricted Formularies," which was held November 4–5, 2002, in Washington, D.C., and supported by an unrestricted educational grant from Eli Lilly and Company.

Corresponding author and reprints: Carol A. Tamminga, M.D., UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9070 (e-mail: carol.tamminga@UTSouthwestern.edu).

With or without treatment, few people with schizophrenia fully return to pre-illness levels of function.[1] Approximately 30% of individuals with schizophrenia show partial but good response to treatment, while another 30% show partial but inadequate response. The remaining 20% to 25% of people with schizophrenia are treatment resistant.

The modern history of treatments for schizophrenia began in the early 20th century with experimental, but ineffective, techniques such as vasectomy, adrenalectomy, and induced fever. In the 1930s, electroconvulsive therapy proved effective in treating psychosis, but this rather extreme measure was eclipsed by the introduction of the first generation of pharmacologic agents for the treatment of schizophrenia in the 1950s, following the serendipitous discovery of chlorpromazine's antipsychotic action. The identification of dopamine receptor blockade as the mechanism of antipsychotic action provided a molecular target for the development of future antipsychotic agents with fewer side effects. Haloperidol was the most successful of these first-generation antipsychotics. The second generation of antipsychotics—clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole—were developed 4 decades later.

Most antipsychotic drugs act equivalently and potently on the positive symptoms of schizophrenia. On the other hand, in populations of persons who are already optimally treated, negative symptoms and cognitive deficits account for the extensive psychosocial dysfunction, and the second-generation drugs seem to be associated with better outcomes with respect to these symptoms areas. In the United States, the majority of the antipsychotic market is composed of second-generation antipsychotics. Each of these has a differing set of pharmacologic characteristics to which individual patients respond differently.

PHARMACOLOGIC CHARACTERISTICS OF ANTIPSYCHOTICS

Haloperidol

Haloperidol was at one time the most prescribed antipsychotic in the world. It is still widely used for its cost advantage, as a comparator drug in effectiveness studies, and in cases where a long-acting drug formulation is preferred. Haloperidol binds strongly to dopamine receptors in the brain. Positron emission tomography (PET) has shown that at clinically relevant doses of haloperidol, dopamine type 2 (D_2) receptor occupancy is 80% to 95%.[1] This high affinity for dopamine receptors is thought to mediate not only the antipsychotic effect of haloperidol but also the parkinsonism and akathisia side effects associated with its use. Haloperidol induces depolarization blockade in both mesolimbic (A10) dopamine neurons and nigrostriatal (A9) dopamine neurons, which may also contribute to movement disturbance. The severity of haloperidol's motor side effects have made it an unpopular drug among schizophrenic patients. Other side effects, however, are low to rare.

The half-life of haloperidol is 12 to 22 hours, and time to maximum concentration (T_{max}) is 5 hours. Research suggests that effective steady-state plasma levels of haloperidol are between 4 and 16 ng/mL.[2] Zimbroff et al.[3] tested doses of 4, 8, and 16 mg/day of haloperidol in a multicenter, controlled trial and found no dose-response relationship to any single symptom, symptom cluster, or motor side effect, suggesting that 4 mg/day may already be beyond the dose-sensitive range for haloperidol.[1] Experts recommend that clinicians initiate treatment with low (2–4 mg/day haloperidol) doses of any first-generation antipsychotic.[4]

Clozapine

Clozapine initiated the era of second-generation antipsychotics, though it differs pharmacologically from those that followed. Clozapine has a broad, low-affinity receptor profile, showing widespread and complex antagonistic action at dopamine, serotonin, norepinephrine, acetylcholine, and histamine receptors. At clinically effective doses, clozapine occupies fewer striatal dopamine receptors (15%–60% depending on the tracer used) than the first-generation antipsychotics.[1] Unlike haloperidol, clozapine has high affinity (80% to 90% receptor occupancy) for serotonin type 2 ($5\text{-}HT_2$) receptors. Clozapine increases regional cerebral blood flow less than haloperidol in the dorsal and ventral striatum but more than haloperidol in the anterior cingulate, which is crucial to attention and executive function, and in the dorsolateral frontal cortex.[5] It has a half-life of 10 hours and T_{max} of 3 hours.

Clozapine is the only antipsychotic to have demonstrated greater antipsychotic efficacy than traditional agents. However, because of its discouraging side-effect profile, clozapine is virtually never a first-line drug. Clozapine is used predominantly in situations of treatment resistance, in which a patient has shown no response to at least 2 different antipsychotic trials. The side effects of clozapine range from the inconvenient, like drooling, to more important effects like tachycardia, weight gain, dyslipidemias, and potentially fatal agranulocytosis. Due to the risk of agranulocytosis, regular blood monitoring is required. Other possible side effects include sedation and seizures. Clozapine causes virtually no motor side effects, possibly because it shows anatomic selectivity and induces depolarization blockade only in the A10 neurons and not in the A9 neurons, which are thought to mediate motor side effects. Clozapine's severe side effects might prevent its use except for the important fact that clozapine alone produces a superior antipsychotic effect on positive symptoms.

Risperidone

Risperidone has a high affinity for both $5\text{-}HT_{2A}$ and D_2 receptors; risperidone's affinity for the former is 20 times higher than its affinity for the latter.[1] Although its effects are largely the result of dopamine and serotonin receptor antagonism, risperidone also has a relatively high affinity for α_1-noradrenergic and histamine type 1 (H_1) receptors. Risperidone exerts greater dopaminergic effects in the frontal cortex than in the striatum. It is thought that increasing the release of dopamine and norepinephrine in the frontal cortex may help improve cognitive deficits. The T_{max} is 1 hour and the half-life is 3.6 hours for risperidone, while the T_{max} is 3 hours and the half-life is 22 hours for risperidone's active metabolite.

In vivo imaging indicates that a 1-mg oral dose of risperidone achieves about 50% D_2 receptor occupancy and about 60% $5\text{-}HT_{2A}$ receptor occupancy.[1] Long-term risperidone treatment at low but clinically effective doses results in a D_2 receptor occupancy of less than 70%,[6] nearing the threshold of high risk for motor disturbances and hyperprolactinemia.[7] Like the older antipsychotics, risperidone induces both A9 and A10 depolarization blockade. At risperidone doses below 6 mg/day, motor side effects are absent, but at doses higher than 6 mg/day, drug-induced motor side effects appear.[1] At high doses—those greater than 10 mg/day—motor side effects may be at the level of those caused by haloperidol. Hyperprolactinemia, with consequences such as galactorrhea, is one of the side effects in patients treated with risperidone.

Olanzapine

The olanzapine molecule is a structural congener of clozapine. Like clozapine, olanzapine is a broad receptor antagonist, but unlike clozapine, olanzapine has high affinity for most sites. Olanzapine has efficacy equivalent (not superior) to haloperidol in treating positive symptoms. Like risperidone, olanzapine exerts a stronger serotonin than dopamine blockade. Olanzapine also has a very

prominent antidepressant action in addition to its antipsychotic effect and for this reason is sometimes used as the drug of choice in affective psychoses.

Measured by PET imaging, the 60% D_2 receptor occupancy of olanzapine is lower than that of the first-generation antipsychotics[1] and below the D_2 receptor occupancy threshold of greater than 70% for acute motor side effects.[8] Its anatomic selectivity for depolarization blockade in A10 dopamine but not A9 dopamine neurons may contribute to olanzapine's low rates of parkinsonism and akathisia. Olanzapine treatment can be associated with an elevation in liver enzymes and with the metabolic syndrome—a combination of weight gain, diabetes, hypertension, and dyslipidemias—affects that it shares with some other atypicals. This latter is an adverse effect which is not experienced by the patient but is accompanied by increased cardiac risk. Olanzapine reaches T_{max} in 5 hours and has a half-life of 31 hours.

Quetiapine

Quetiapine is from the dibenzothiazepine class but, like clozapine, has low affinity for a broad range of neurotransmitter receptors, including serotonergic, dopaminergic, histaminergic, and adrenergic receptors. PET imaging has shown that quetiapine has only a transient occupancy at D_2 receptors.[9] A recent study[9] found that administration of a clinically relevant single dose of quetiapine in psychotic patients resulted in a mean peak D_2 receptor occupancy of approximately 62% 2 hours postdose, which declined to approximately 14% about 20 hours postdose. High rates of response among these patients raised the question whether continuously high D_2 receptor occupancy is necessary for antipsychotic effect. In other research,[1] quetiapine D_2 receptor occupancy in the striatum has been measured at 44% 2 hours postdose and 27% 12 hours postdose, while quetiapine occupancy in the cortex at serotonin receptors was 72% 2 hours postdose, declining to 50% 24 hours postdose.

In addition to transiently high D_2 receptor occupancy, quetiapine exhibits anatomic selectivity that may reduce the risk of motor side effects. Quetiapine may cause somnolence (likely attributable to H_1 receptor occupancy), headache, and some weight gain. It has a T_{max} of 1.5 hours and a half-life of 6 hours.

Ziprasidone

Like other second-generation antipsychotics, ziprasidone's action at serotonergic receptors is considerably greater than its action at dopaminergic sites. However, the broad receptor-binding profile of ziprasidone uniquely includes the norepinephrine and dopamine reuptake proteins, which explains the drug's usefulness in treating schizophrenia with serious depression. In vivo imaging performed on healthy volunteers 4 hours after a 40-mg oral dose of ziprasidone revealed D_2 receptor occupancy of approximately 79% and serotonin receptor occupancy of 98%.[1]

Although ziprasidone has relatively high rates of D_2 receptor occupancy as well as A9 and A10 depolarization blockade, rates of parkinsonism and akathisia are quite low. There is no weight gain associated with ziprasidone treatment, even after lengthy treatment. The most serious side effect of ziprasidone, which postponed its presence on the market for a year, is the cardiac characteristic of QTc prolongation; although this can imply greater cardiac risk, safety studies in large patient cohorts failed to show any greater cardiac risk or any increase in "all cause" mortality with the drug. The half-life of ziprasidone is 10 hours, and the T_{max} is 4.7 hours.

Aripiprazole

Aripiprazole is the newest antipsychotic on the market. Like other second-generation antipsychotics, aripiprazole exhibits high affinity for the D_2 and 5-HT_{2A} receptors. However, it is unique in acting as a partial dopamine agonist. In addition to blockade at the dopamine receptor, this drug provides blockade with a small amount of agonist action. Aripiprazole's partial agonist effects at the 5-HT_{1A} receptor, in addition, may contribute to anxiolytic or antidepressant effects. Aripiprazole has modest affinity for α_1-adrenergic and H_1 receptors. It has a long half-life of 75 hours and a T_{max} of 3 to 5 hours. Due to the recent introduction of this drug, which may herald the next new class of antipsychotic agents, there is at present little clinical information regarding important side effects associated with aripiprazole treatment, except that it fails to cause either hyperprolactinemia or significant weight gain.

CHOOSING AND SWITCHING

For many years, it was suggested that physicians should employ long-acting formulations, available until lately only among first-generation antipsychotics, in order to increase patients' adherence. While there is no way to ensure adherence among patients with schizophrenia, the milder side effect profiles of the second-generation antipsychotics should ideally reduce nonadherence attributable to intolerable side effects. Due to the differences among antipsychotics available today, optimizing treatment for individual patients requires case-by-case assessment on the part of the clinician to choose the most appropriate drug and, if necessary, to switch to a different drug if the first proves unsatisfactory.

The treating physician must carefully match the diverse needs of schizophrenic patients with the varied characteristics of the second-generation antipsychotics. For example, a young, highly agitated man of normal weight who has high psychosis ratings and a past history of treatment resistance may be a good candidate for clozapine. This patient's normal weight places him at relatively low

risk for drug-induced obesity, and the fact that he is highly agitated suggests that he may benefit from the side effect of sedation. Most importantly, this patient is afflicted by severe positive symptoms and has failed to respond to other antipsychotics in the past; these cues point to clozapine for its superior antipsychotic efficacy.

What might be the best antipsychotic choice for a 30-year-old man who is hospitalized with schizophrenia and has been unresponsive to previous treatments? Again, for any treatment-resistant patient—and particularly for such a patient who is already hospitalized, which enables monitoring for agranulocytosis—clozapine is a rational treatment choice.

However, for a slightly overweight middle-aged woman who is stabilized but requires chronic treatment, clozapine would not be a good match. Risperidone, which has less risk of weight gain, may be a good choice of antipsychotic for this patient. If such a patient has serious depression in addition to psychosis, ziprasidone may be a more preferable choice.

Physicians may switch drugs for the possibility of greater efficacy or because a particular side effect profile is unacceptable. Patients with schizophrenia may be switched from first-generation to second-generation antipsychotics in order to decrease motor side effects, to lessen drug-induced dysphoria, or possibly to increase adherence. A physician may switch a patient from risperidone to olanzapine or ziprasidone because the patient finds parkinsonism or galactorrhea intolerable. Likewise, a switch from another atypical to olanzapine might be indicated in the presence of significant depressive symptoms and/or cognitive dysfunction. A switch from olanzapine to quetiapine may offer the beneficial side effect of sedation to a highly agitated patient. A switch to clozapine offers greater antipsychotic efficacy but also increases the risk of serious side effects. For this reason, clozapine, despite its superior antipsychotic efficacy, may be underutilized in the treatment of schizophrenia today.

CONCLUSION

Most antipsychotic drugs act equivalently and potently on the positive symptoms of schizophrenia, leaving negative symptoms and cognitive deficits as the remaining targets. The second-generation drugs are associated with reduced negative symptoms and cognitive dysfunction, which may, in part, be related to relief from some of the effects of older drugs. Although all second-generation antipsychotics work via dopamine and serotonin receptors, each has a different set of pharmacologic characteristics, including side effects. Due to the differences among antipsychotics available today, optimizing treatment for individual patients requires choosing the most appropriate drug and, if necessary, switching to a different drug if the first proves unsatisfactory. The treating physician must carefully match the diverse needs of schizophrenic patients with the varied characteristics of the second-generation antipsychotics.

Drug names: aripiprazole (Abilify), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Tamminga CA. Principles of the pharmacotherapy of schizophrenia. In: Charney DS, Nestler EJ, Bunney BS, eds. Neurobiology of Mental Illness, pt 3: Psychoses. 2nd ed. New York, NY: Oxford University Press; 1999
2. Van Putten T, Marder SR, Wirshing WC, et al. Neuroleptic plasma levels. Schizophr Bull 1991;17:197–216
3. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997;154:782–791
4. Kapur S, Remington G, Jones C, et al. High levels of dopamine D_2 receptor occupancy with low-dose haloperidol treatment: a PET study. Am J Psychiatry 1996;153:948–950
5. Lahti AC, Holcomb HH, Weiler MA, et al. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. Biol Psychiatry 2003;53:601–608
6. Nyberg S, Farde L, Erikssen L. 5-HT2 and D2 dopamine receptor occupancy in the living human brain. Psychopharmacology (Berl) 1993;110:265–272
7. Tauscher J, Kapur S. Choosing the right dose of antipsychotics in schizophrenia: lessons from neuroimaging studies. CNS Drugs 2001;15: 671–678
8. 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: relation to extrapyramidal side effects. Arch Gen Psychiatry 1992;49:538–544
9. Tauscher-Wisniewski S, Kapur S, Tauscher J, et al. Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. J Clin Psychiatry 2002;63:992–997

Note from the Chair: As this article was going to press, the U.S. Food and Drug Administration (FDA) and Health Canada issued directives that, as a class, atypical antipsychotics must carry a warning about the risk of weight gain and type 2 diabetes. The manufacturers of ziprasidone and aripiprazole have petitioned the FDA seeking to exclude these 2 drugs from this required warning.