Schizophrenia is an illness that has been recognized for millennia; despite this, the discovery of medications for its treatment has occurred only in the past half century (Carpenter and Buchanan, 1994). Neither the etiology of schizophrenia nor its pathophysiology has been clarified; nonetheless, empirical treatments that provide considerable symptomatic benefit are available (Davis, 1969; Tamminga, 1997). Theoretical strategies for new drug development have been proposed and are currently being used to identify new compounds (Creese, 1976; Robertson et al., 1994; Meltzer, 1995; Grace et al., 1997). Based on these strategies, effective antipsychotic drugs have appeared and have vastly improved symptom manifestations and outcome in schizophrenia; moreover, this process shows further promise for the development of new therapies (Tamminga, 2002).

This chapter will focus first on a review of the symptomatic dysfunctions that are the target for antipsychotic treatment, then on representative traditional and new drugs available for use, and finally on practical points for effective treatment.

TARGET SYMPTOMS FOR PHARMACOTHERAPY

Schizophrenic symptoms manifested by individuals affected by the illness include positive psychotic symptoms that are prominent during acute periods, but also cognitive dysfunction and negative symptoms. The World Health Organization (WHO), in its 1971 pilot study, looked at symptom type and frequency in several countries (Sartorius et al., 1974). The WHO list of the most frequent acute psychotic symptoms (Table 25.1) identifies characteristics of the illness that require treatment. Acute psychotic symptoms do not vary by sex, by presentation, or by geographical region. The symptom identified as “lack of insight” is nearly ubiquitous among schizophrenic persons and is highly crippling. This descriptor means that schizophrenic persons experience their psychotic perceptions as real sensory information. Not only are schizophrenics troubled by involuntary thoughts and sensory experiences, but they identify the psychotic experiences as true events in their lives. Treatments that could merely convert these “real-life experiences” into symptoms, and dissociate their meaning from relevance to the schizophrenic person, could vastly improve the patient’s outcome. Traditional antipsychotics can do this to some extent; clozapine may be superior in this regard.

Several large factor analytic studies of symptoms in representative treated and stable schizophrenic populations have consistently reported three clusters of symptoms in the illness: (1) positive psychotic symptoms (e.g., hallucinations, delusions, and paranoia), (2) reality distortion (e.g., thought disorder and bizarre behavior), and (3) negative symptoms (e.g., anhedonia, asociality, and alogia) (Carpenter and Buchanan, 1994). In addition, evidence of cognitive dysfunction in schizophrenia is ubiquitous (e.g., attention and short-term memory impairments). Any one of these symptom clusters can express itself predominantly in an individual, even though all symptoms may be present at some level. Whether these clusters represent distinct but related illnesses (e.g., like symptoms of chronic heart failure) or a single illness with multiple manifestations (e.g., like symptoms of diabetes), is frequently debated. Although these domains have been phenomenologically derived, subsequent testing has identified several psychological, physiological, and functional group differences that are consistent with a distinct biology (Carpenter et al., 1993).

With respect to treatment, different symptom tracts in schizophrenia respond differently to pharmacotherapy. Hallucinations, delusions, paranoia, and thought disorder show an overall good response to traditional and new antipsychotics. Both cognitive dysfunction and negative symptoms are poorly responsive, if at all, to treatment. Cognitive dysfunction, particularly poor verbal memory and/or reduced vigilance, predicts broad overall failure in long-term psychosocial rehabilitation. Negative symptoms predict poor social problem solving, but not necessarily poor community functioning or low skill acquisition (Green, 1996). Since enduring negative symptoms and cognitive dysfunction impact crit-
Table 25.1 Frequency of Psychotic Symptoms in Schizophrenia (WHO International Pilot Study)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Lack of insight</td>
<td>97%</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>74%</td>
</tr>
<tr>
<td>Verbal hallucinations</td>
<td>70%</td>
</tr>
<tr>
<td>Ideas of reference</td>
<td>70%</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>65%</td>
</tr>
<tr>
<td>Flatness of affect</td>
<td>65%</td>
</tr>
<tr>
<td>Voices speaking</td>
<td>65%</td>
</tr>
<tr>
<td>Paranoid state</td>
<td>64%</td>
</tr>
<tr>
<td>Thought alienation</td>
<td>52%</td>
</tr>
<tr>
<td>Thoughts spoken aloud</td>
<td>50%</td>
</tr>
</tbody>
</table>


Trichotic symptoms in bipolar mania, psychotic disorders in multiple diagnostic categories. Positive symptoms of the illness. Only 5%-10% of schizophrenic persons go on to achieve a full recovery with or without these medications. Some 30% show a good but partial response, and another 30% show an inadequate but partial response. The remaining 20%-25% of schizophrenic persons are resistant to treatment with any antipsychotic drugs. These treatment-resistant schizophrenics suffer considerably and use a disproportionate amount of health care services. Thus their treatment is a priority.

Antipsychotic drugs, as their name implies, treat psychosis in multiple diagnostic categories. Positive psychotic symptoms in bipolar mania, psychotic depression, and dementia with psychosis all respond positively to the antipsychotic treatments described here and are the indicated drugs in these disorders. Schizophrenia characteristically requires continuous treatment for decades, whereas these other psychotic illnesses usually require only targeted treatment during active psychotic phases. Moreover, certain patient groups are more susceptible to the motor side effects of antipsychotic drugs, such as the elderly and those with mood disorder diagnoses (Kane and Smith, 1982). Dosing considerations are comparable, with accommodation for age and size, especially in the elderly and in children.

Traditional Antipsychotic Drugs

The antipsychotic action of the first neuroleptic, chlorpromazine, was discovered serendipitously when the drug was first tested in France by Delay and Deniker (1952) as a sedative agent for schizophrenia. Its selective antipsychotic properties were quickly noted. In the decade following this discovery, not only was the probable mechanism of antipsychotic drug action articulated as dopamine receptor blockade (Carlsson and Lindquist, 1963), but many additional antipsychotic compounds were generated. These drugs have formed the traditional antipsychotic drug armamentarium for psychiatrists throughout the past half century. Each of the traditional antipsychotics is associated with a different side effect profile but with the same primary antipsychotic actions (Davis, 1969).

Apart from historical interest, there are several reasons to remain interested in traditional antipsychotics today, including their demonstrated effectiveness in treating the psychosis of schizophrenia and their economic advantage. Moreover, considerably more clinical prescribing experience exists for the traditional antipsychotics than for the new drugs.

Chlorpromazine (Thorazine)

Chlorpromazine was developed by Rhône-Poulenc and first tested in the United States in the early 1950s in several large multicenter trials (Davis, 1969). These trials inevitably included drug-naive individuals because this was the first effective drug treatment for psychosis. The response was brisk and extensive; full improvement gradually occurred over several weeks. Reductions of 80% or more in symptom profiles occurred commonly, including hallucinations, delusions, and thought disorder. The residual symptoms in the negative and cognitive domains were not immediately noted because of the extensive response of positive symptoms. It is no wonder that this drug was widely applied and the development of additional compounds encouraged by these data, because of its overall efficacy in treating florid psychosis.

Side effects of chlorpromazine included not only parkinsonism and akathisia, but also hypotension, sedation, constipation, weight gain, and amenorrhea. Hepatotoxicity, electrocardiographic changes, and seizures were less frequent but more serious side effects. Changes in skin color with sun exposure and retinal changes were described. Tardive dyskinesia occurred as well. Today the use of chlorpromazine has gradually diminished, based mostly on its sedation, cardiovascular side effects, and still significant parkinsonism, but it has not disappeared entirely.

Haloperidol (Haldol)

Haloperidol was developed by Janssen Pharmaceutical Company in the 1950s. Until very recently, it was the most widely used antipsychotic for the treatment of schizophrenia. Its potent antipsychotic action with lit-
tle sedation, despite considerable motor side effects, has sustained its widespread use. Today, these same characteristics, coupled with its relative economic advantage, keep it a viable antipsychotic treatment. It remains to be seen if the new neuroleptics will offer such side effect advantages over haloperidol to increase compliance and reduce relapse sufficiently to balance their increased cost.

**Pharmacology**

The pharmacology of haloperidol is extensively documented because the drug is widely used as the prototypical comparator antipsychotic. Therefore, it will be profiled here as an example of a traditional antipsychotic. Haloperidol has a high affinity for the D₂ family of dopamine receptors (D₂, D₃, and D₄) and for the sigma binding site; it possesses measurable affinity for the 5-hydroxytryptamine₂A (5-HT₂A) serotonin and α₁-noradrenergic receptors, but these affinities may not be relevant at doses used clinically (Table 25.2). Haloperidol possesses all the classic pharmacological properties of an antipsychotic agent: it inhibits conditioned avoidance responding, blocks apomorphine- and amphetamine-induced behaviors, and it induces catalepsy in animal preparations. It elevates dopamine metabolites in both the rat dorsal striatum and nucleus accumbens with acute administration (Fink-Jensen et al., 1996). It causes depolarization blockade in the both the nigrostriatal (A9) and mesolimbic (A10) dopamine neurons with subchronic treatment (Grace et al., 1997); moreover, it stimulates Fos protein expression in striatal dopamine terminal areas as well as in limbic target regions with acute administration (Robertson et al., 1994). Subchronic treatment in laboratory animals up-regulates D₂ dopamine receptors in striatum, increases γ-aminobutyric acid A (GABA_A) receptor sites in the substantia nigra pars reticulata, and modifies GABA_A receptor binding in thalamus (Shirakawa and Tamminga, 1994). Several of these pharmacological actions of haloperidol in animals have been linked with the ability of haloperidol to induce parkinsonism and akathisia in humans, like catalepsy, nonselective (i.e., both A9 and A10 dopamine neurons) depolarization blockade, and striatal Fos stimulation; these latter characteristics have become undesirable in the laboratory screening of antipsychotic drugs.

**Metabolism and pharmacokinetics**

How a drug is metabolized and eliminated from active drug pools in the body should influence prescribing patterns for the compound and dictate dosing modifications in special situations. Haloperidol is a good example of an antipsychotic for this purpose because it has only one minor, inactive metabolite (reduced haloperidol) and its plasma levels are straightforward to analyze. Reduced haloperidol is the major single metabolite of haloperidol, and its affinity at the dopamine receptors is low. Haloperidol’s half-life (T₁/₂) is 12–22 hours in a mixed schizophrenic population; in “good” metabolizers, haloperidol has a half-life of 12.2 ± 2.6 hours. In a typical population (N = 10), the time to maximum concentration (T_max) of haloperidol was found to be 5 ± 2 hours, and its distribution half-life (T_d) was 1.3 ± .03 hours; the peak plasma level (C_max)

<table>
<thead>
<tr>
<th>Table 25.2 In Vitro Receptor Binding (Affinity Values Ki in nM)</th>
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<tbody>
<tr>
<td><strong>D1</strong></td>
</tr>
<tr>
<td><strong>D2</strong></td>
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<tr>
<td><strong>D3</strong></td>
</tr>
<tr>
<td><strong>D4</strong></td>
</tr>
<tr>
<td><strong>5-HT₂A</strong></td>
</tr>
<tr>
<td><strong>5-HT₁A</strong></td>
</tr>
<tr>
<td><strong>5-HT₂C</strong></td>
</tr>
<tr>
<td><strong>5-HT₁D</strong></td>
</tr>
<tr>
<td><strong>5-HT reuptake</strong></td>
</tr>
<tr>
<td><strong>NE reuptake</strong></td>
</tr>
<tr>
<td><strong>a₁</strong></td>
</tr>
<tr>
<td><strong>a₂</strong></td>
</tr>
<tr>
<td><strong>H₁</strong></td>
</tr>
<tr>
<td><strong>5-HT₆</strong></td>
</tr>
<tr>
<td><strong>5-HT₇</strong></td>
</tr>
<tr>
<td><strong>Muscarnic</strong></td>
</tr>
</tbody>
</table>

*Source: The data in this table were taken from the following references and compiled by Dr. Robert A. Lahti (Leysen et al., 1994; Bymaster et al., 1996; Lahti, 1996).*  
5-HT: 5-hydroxytryptamine; NE: norepinephrine.
after a 10 mg oral concentrate was 12.3 ± 6.7 ng/ml; the elimination half-life ($T_{1/2}$) was 21.7 ± 20 hours. None of these acute or chronic kinetic parameters correlate with the clinical response to the drug (C.A. Tamminga, unpublished data). Multiple treatment studies suggest that effective steady-state drug plasma levels are 4–16 ng/ml (VanPutten et al., 1991).

**In vivo imaging**

Haloperidol fully occupies the striatal D$_2$ receptors at clinically effective doses, at levels of 80%–95% measured using $^{11}$C-raclopride ($^{11}$C-RAC) and positron emission tomography (PET). This level of occupancy has been documented in all patient groups evaluated, even in treatment-resistant schizophrenics. The high D$_2$ occupancy of haloperidol has suggested this as a mechanism not only for its antipsychotic action but also for its parkinsonism and akathisia side effects. Because full haloperidol occupancy of 80%–95% is present from the beginning of drug administration, what accounts for the prolonged time to full antipsychotic action?

Haloperidol occupancy of the striatal D$_2$ receptor in schizophrenic patients is dose dependent; furthermore, measurable occupancy of the D$_2$ receptor with chronic treatment remains approximately 1 week after drug withdrawal and dissipates by 2 weeks (Tamminga et al., 1993). Haloperidol lacks measurable occupancy at the cortical 5-HT$_2$ receptor using PET with $^{11}$C-N-methylspiperone ($^{11}$C-NMSP).

Functional imaging studies have addressed the question of where in the central nervous system (CNS) haloperidol exerts its actions (Holcomb et al., 1996). Our own work in this area has shown that haloperidol increases neuronal activity in the human striatum, both dorsal and ventral, measured using $^{15}$O-water and PET for quantifying regional cerebral blood flow (rCBF) (Fig. 25.1). In addition, haloperidol increases neuronal activity in the thalamus and decreases glucose metabolism in the frontal cortex and anterior cingulate with no other regional alterations in the CNS (Holcomb et al., 1996). Two aspects of these results have determined our interpretation of haloperidol's mechanism of antipsychotic action: one is that haloperidol causes a different direction of neuronal activation regionally; the other is that haloperidol causes effects in areas with few or no dopamine receptors (i.e., thalamus). Thus, we have speculated that haloperidol reduces psychosis by exerting its primary action in the caudate/putamen (blockade of D$_2$ dopamine receptors) and that this action is transmitted to other CNS regions by the well-described neuronal circuits connecting the basal ganglia, thalamus, and cortex (Alexander and Crutcher, 1990). While actions of other antipsychotics at other receptor sites (e.g., serotonin receptors) may be exerted primarily in cortex, we speculate that the antidopaminergic actions of antipsychotics are initiated in the striatum and then transmitted in a secondary and tertiary manner to cortex through the brain's own neural pathways (Alexander and Crutcher, 1990). Alternatively, haloperidol could have a primary action in multiple different brain regions to deliver its clinical effect.

Evaluation of the acute action of haloperidol on rCBF dynamically using $^{15}$O-water with PET captures the regional time course of haloperidol's action (Fig. 25.2). The rCBF changes in these areas are sustained over time and represent a pharmacodynamic measure of drug action at their site of action. These data show that distinct cerebral regions display distinct dynamic rCBF patterns in direction and in time course. Certain of these patterns should predict specific aspects of drug action; we have recently shown that rCBF changes over time correlate with the clinical response.

**Efficacy**

The antipsychotic efficacy of haloperidol was initially established in controlled trials in the early 1960s...
FIGURE 25.2 Pharmacodynamic and psychokinetic analysis of an acute dose of haloperidol (10 mg). The dynamic regional cerebral blood flow (rCBF) effect is shown in caudate and thalamus from positron emission tomography-O-15 water scans (N = 6) taken over 12 hours after drug. Haloperidol drug levels in plasma are analyzed over the same time course using mass spectroscopy. The rCBF remains elevated in basal ganglia and thalamus across the entire drug half-life. Courtesy of Dr. Adrienne Lahti.

(Davis, 1969); it is a highly effective antipsychotic, useful at low doses. But it was not until recently that a dose-response study was conducted across the apparent dose-sensitive range for haloperidol. Three doses of haloperidol (4, 8, and 16 mg/day) were tested against placebo in a multicenter controlled trial (Zimbroff et al., 1997). The study results showed haloperidol to be a highly efficacious antipsychotic in schizophrenia, with significant action across all the selected doses; moreover, there was no linear dose-response relationship in any symptom or symptom cluster across this dose range. The lack of a dose-response correlation in this study suggests either (or both) of the following: that the standard multicenter trial design is too insensitive to detect dose differences for antipsychotics routinely or that 4 mg/day is already beyond the dose-sensitive range for haloperidol. If the latter is true, treatment with haloperidol by many psychiatrists has used doses that are far too high. If large multicenter trial designs are insensitive, new approaches need to be developed to test more subtle yet highly clinically relevant features of drug action.

**Side effects and safety**

In the above dose study, haloperidol produced significant parkinsonism on the Simpson-Angus Scale (SAS) and akathisia on the Barnes Akathisia Scale (BAS) across all the doses used, even at the lowest dose of 4 mg/day. There were no relationships between drug dose and motor side effects in the 4–16 mg/day range. Other side effects of haloperidol were low, including cardiovascular, anticholinergic, and hematological. No QTc prolongation occurs with haloperidol. Hepatotoxicity was a rare side effect. These safety results are consistent with years of clinical experience using haloperidol.
NEW ANTIPSYCHOTICS: BROAD PROFILE RECEPTOR ANTAGONISTS

Antipsychotic drugs that block many monoamine and other G protein–coupled receptors in brain have a broad receptor affinity profile (Table 25.2). Their spectrum of receptor antagonist activity is extensive, and their overall clinical action is neurochemically complex.

Clozapine (Clozaril)

Clozapine is an antipsychotic drug developed by Novartis (Sandoz), which, although it has led the "new drug" era, is not itself new. At its initial application, clozapine was not fully recognized as having a unique clinical action. Its demonstration of superior efficacy over chlorpromazine in treatment-resistant schizophrenic patients spurred subsequent research in this area (Kane et al., 1988). It is the only antipsychotic shown so far to have superior antipsychotic action in schizophrenia compared with the traditional and the new compounds. Its mechanism in this regard remains unknown.

Pharmacology

Clozapine has an affinity for a broad array of monoaminergic and other receptors in brain. Not only the dopamine receptors (D1, D5, D2, D3, D4,) but also serotonin (5-HT2A, 5-HT2C, 5-HT6, 5-HT7), norepinephrine (α1 and α2), cholinergic (nicotine and muscarinic), and histamine (H1) receptors are blocked by clozapine. Clozapine affinities are generally low at all sites (Table 25.2). In laboratory behavioral studies, clozapine blocks not only dopamine agonist–stimulated responses but also cholinergic-, serotonergic-, and noradrenergic-stimulated neurochemical and behavioral actions in animals. Clozapine inhibits conditioned avoidance behavior but does not produce catalepsy. Clozapine does not measurably alter dopamine metabolite concentrations in striatum but does increase (DOPAC) in the rat nucleus accumbens (Coward, 1992).

Clozapine was the first antipsychotic shown to have anatomically selective electrophysiological actions on dopamine neurons; clozapine induces depolarization blockade in the mesolimbic (A10) dopamine neurons but not in the nigrostriatal (A9) cells (Grace et al., 1997). The association of this distinctive preclinical characteristic with the drug’s low motor side effect profile in human use is broadly consistent with the idea that antipsychotic actions are generally mediated through the mesolimbic (A10) dopaminergic neurons and motor side effects through the A9 group. Consistent with clozapine’s action in the depolarization inactivation model, has been its selective functional anatomic using c-fos in situ hybridization autoradiography and Fos protein immunohistochemistry (Robertson et al., 1994). These studies show that clozapine stimulates immediate early gene (IEG) expression in rats in mesolimbic projection fields of the dopamine cell bodies (nucleus accumbens, ventral striatum, anterior cingulate, and medial prefrontal cortex) but not in the nigrostriatal projections to the dorsal striatum (A9). The mechanism subserving this anatomical selectivity of clozapine’s action remains unknown. Nonetheless, the principle that limited regional drug action in CNS is important to schizophrenia pharmacology has been repeatedly demonstrated. Moreover, the failure of clozapine to induce dyskinesias in the neuroleptic-sensitized monkey (Casey, 1996) or to cause oral dyskinesias in chronically treated rats (Gunne et al., 1982) is consistent with these observations.

Metabolism and pharmacokinetics

Clozapine has several metabolites, two of which are norclozapine and desmethylclozapine. Too little data are available on clozapine metabolism and the activity of its metabolites. Single-dose kinetic analysis with a 200 mg oral dose of clozapine found the T<sub>max</sub> to be 3 ± 1.5 hours and the C<sub>max</sub> to be 386 ± 249 ng/ml. The distribution half-life (T<sub>1/2</sub>) is 0.1 ± .12 hours, and the elimination half-life (T<sub>β1/2</sub>) is 10.3 ± 2.9 hours. Plasma concentrations show a linear relationship to dose with multiple dose kinetics. Terminal elimination is linear.

In vivo imaging

Clozapine occupies measurably fewer striatal dopamine receptors at clinically effective doses than do traditional neuroleptics (Farde et al., 1992). Using <sup>1</sup> C-RAC and PET, occupancy is 40%–60%; with <sup>1</sup> C-NMSP, occupancy is 15%–30%. The difference in these absolute occupancy levels is generally ascribed to the different affinities of the two tracers for the dopamine receptor. Clozapine occupies 80%–90% of serotonin receptors in cortex measured with <sup>1</sup> C-NMSP, consistent with its in vitro affinity profile. The profile of reduced dopamine receptor occupancy in striatum and increased serotonin receptor occupancy in cortex is characteristic of the new generation of antipsychotic (Kapur et al., 1999).

Functional imaging results demonstrate the regional actions of the drug in human brain. Like haloperidol, clozapine increases rCBF in striatum, but only in its ventral aspect and to a lesser extent (Fig. 25.3A). Moreover, clozapine differs from haloperidol in that it increases neuronal activation in the anterior cingulate...
cortex and in the middle frontal gyrus, areas that are important to core cognitive functions like attention and working memory (Fig. 25.3B). During task performance, clozapine “normalizes” rCBF in several areas of frontal cortex, especially in the anterior cingulate cortex (Lahti et al., 2003). These broad differences in cerebral activation patterns between clozapine and haloperidol likely represent in some way the unique clinical action of clozapine in schizophrenia and could, with further study be developed as a surrogate marker of that action.

Efficacy

The general antipsychotic efficacy of clozapine was established more than 20 years ago. However, to achieve a commercial market in the United States, Sandoz was required to demonstrate its superiority to traditional antipsychotics due to the drug’s serious agranulocytosis risk. This was done by Kane and colleagues (1988) in a multicenter design, where clozapine was demonstrated to be superior to chlorpromazine in treating treatment-refractory schizophrenic inpatients. Subsequently, several additional studies confirmed this unique action (Conley et al., 1997a). Moreover, superior efficacy in partially nonresponding populations was demonstrated (Kane et al., 2001). This is the only superior antipsychotic with respect to efficacy. Whether clozapine has superior efficacy in treating primary negative symptoms has been widely debated; the answer is suggested but is still not clear. Optimal studies where drug action on negative symptoms can be clearly differentiated from secondary effects or lack of drug side effects have not yet been reported. Some cognitive dysfunctions are improved by clozapine, and others are worsened. Although the final composite outcomes remain to be demonstrated, the long-term psychosocial improvement with clozapine suggests cognitive improvement. There is no doubt that clozapine increases discharge rates from hospital care and improves community function after discharge (Love et al., 1999).

Side effects and safety

Acute motor side effects with clozapine are very low, if detectable at all, including parkinsonism rated with the SAS or akathisia rated with the BAS; all experimental data gathered to date are consistent with clinical experience in this regard. In addition, clozapine appears by all estimates to have an extremely low (if any) incidence of tardive dyskinesia. Moreover, clozapine, when administered to schizophrenics with tardive dyskinesia, allows dyskinetic symptoms to fade gradually over 6–12 months (Tamminga et al., 1994).

With respect to other side effects, clozapine is at the top of any list. It causes agranulocytosis with an incidence of 0.5%–1%, a condition that has a 3%–15% mortality. The risk of agranulocytosis is highest in the second and third months after beginning treatment; the risk is reduced after the first 6 months and remains flat and relatively low after the first 12 months of treatment. In addition, the drug can induce seizures, increase heart rate, and stimulate cardiac arrhythmias. It causes weight gain, substantial in some instances, and alters carbohydrate metabolism and plasma lipid levels (Allison et al., 1999; Wirshing et al., 1999; Henderson et al., 2000). It also causes other, less medically significant but bothersome side effects like sedation and drooling. It is surprising that, with this serious side effect profile, clozapine is used at all; however, the value of its added benefit in psychosis weighs very successfully against all of these side effects, particularly in the seriously ill schizophrenic. Its superior efficacy is the reason, in those situations where efficacy is needed, that the drug’s substantial side effect profile is tolerated. Moreover, many clinicians contend that the drug is un-
derused and that expanded use would provide broader antipsychotic benefits.

Olanzapine (Zyprexa)

Olanzapine was developed and is marketed by Lilly Pharmaceuticals. It is a structural congener of clozapine. It is the third of the new antipsychotics available, preceded to market by clozapine and risperidone. As would be predicted from its pharmacology, olanzapine has many of the same pharmacological characteristics as clozapine, with several significant exceptions in terms of side effects (i.e., no agranulocytosis) and efficacy (i.e., equal but not superior efficacy). However, these ways in which olanzapine differs from clozapine may be highly informative.

Pharmacology

Olanzapine at clinically relevant concentrations has a high affinity for a broad range of CNS receptors, including dopamine (D1–D5), serotonin (5-HT1A, 5-HT2A, 5-HT2C, 5-HT6), noradrenalin (α1), acetylcholine (muscarinic, particularly M1), and histamine (H1) receptors. It is a potent ligand at all of these receptors, with a high affinity at each site (Table 25.2). Different from clozapine, it lacks high affinity for the 5-HT7, α2, and other cholinergic receptors (Bymaster et al., 1996). Olanzapine blocks conditioned avoidance responding in rats but causes catalepsy only at high doses.

Olanzapine increases dopamine and norepinephrine metabolite levels in nucleus accumbens and reduces acetylcholine levels in striatum. Moreover, unlike haloperidol, olanzapine also increases dopamine and norepinephrine release in frontal cortex (Bymaster et al., 1996). Olanzapine blocks dopamine and serotonin-stimulated biochemical changes and animal behaviors; its antiserotonin actions are more potent than its antidopaminergic actions. With chronic treatment, olanzapine significantly but minimally up-regulates D2 receptors in striatum (Sakai et al., submitted). In addition, olanzapine, like clozapine, exerts a regional action on dopamine-containing neurons. With chronic treatment, olanzapine produces depolarization blockade in A10 dopamine neurons but not in the A9 cells (Skarsfeldt, 1995). Olanzapine also shows selective activation of the c-fos IEG gene in ventral striatum and in medial prefrontal cortex without inducing c-fos mRNA in the dorsal striatum (Robertson and Fibiger, 1996). Consistent with this regional action, olanzapine produces dystonias in neuroleptic-sensitized monkeys only at high doses, above its clinically effective dose ranges (Casey, 1996), and fails to produce a high rate of oral dyskinesias (purposeless chewing) in chronically treated rats (Sakai et al., 2001).

Metabolism and pharmacokinetics

Olanzapine has two primary metabolites, 4-N-desmethyl olanzapine and 10-N-glucuronide olanzapine, both of which are inactive as antipsychotics. The parent drug has weak affinity for several different hepatic isoenzyme systems, including CYP-2D6, -1A2, -34A, and -2C19; thus, significant drug-drug interactions on this basis are minimal. T1/2 for olanzapine is 5 hours, and the drug has a mean plasma elimination half-life (T1/2) of 31 hours (range: 21–54 hours). Plasma kinetic studies suggest linear dose proportionality. Female subjects show slower metabolism and consequently higher plasma levels than male subjects. Concurrent cigarette smoking and carbamezapine use accelerate metabolism and lower olanzapine levels modestly.

In vivo imaging

In preliminary human PET studies, olanzapine shows approximately 60% occupancy at the striatal D2 receptors when evaluated with 11C-RAC and PET after an acute 10 mg dose (Farde et al., 1997), a lower striatal dopamine receptor occupancy than that of the traditional antipsychotics. The low motor side effects seen with olanzapine are consistent with the Farde et al. (1992) proposition that it takes a D2 occupancy greater than 70% to induce acute motor side effects. More recent occupancy studies with olanzapine are consistent with these early data (Kapur et al., 1998).

In preliminary studies comparing the functional activation properties of olanzapine to those of haloperidol, it is easy to see that olanzapine is associated with reduced rCBF activation in basal ganglia and thalamus, like clozapine (Fig. 25.4A), and increased rCBF activation in anterior cingulate and temporal cortex, also like clozapine (Fig. 25.4B).

Efficacy

Olanzapine was approved for use based on four large placebo- and haloperidol-controlled multicenter registration trials (Beasley et al., 1997; Tamminga and Kane, 1997). Consistently in all of these trials, olanzapine showed a substantial antipsychotic response in actively psychotic schizophrenic patients, significantly greater than that of placebo on both positive and negative symptoms, and equivalent to that of haloperidol on positive symptoms. There was an indication that olanzapine is more effective than haloperidol in treating negative symptoms. Whether the antinegative symptom response to olanzapine involves primary or secondary negative symptoms has been debated; the results of a path analysis are consistent with a drug action on primary negative symptoms (Tollefson et al., 1997). Further work...
in this area is needed to distinguish the primary from the secondary nature of its negative symptom action. In treatment-resistant schizophrenic inpatients, olanzapine has been compared to chlorpromazine in a design patterned after the clozapine-chlorpromazine trial (Kane et al., 1988). At a fixed dose of 25 mg/day, the action of olanzapine on psychotic symptoms was found to be similar to the action of chlorpromazine; no significant differences in efficacy on psychosis emerged between the two drugs in this population, except that olanzapine imparted a significant antianxiety effect (Conley et al., 1997b). In addition to schizophrenia, olanzapine currently has an indication in the treatment of mania (Tohen and Zarate, 1998).

Side effects and safety
Motor side effects with olanzapine are remarkably and significantly diminished from those seen with haloperidol (Beasley et al., 1996; Tamminga and Kane, 1997). This finding is consistent across studies, thus providing confidence from replication. On average in the controlled trials, parkinsonism (SAS) and akathisia (BAS) were equivalent to placebo and lower than with haloperidol. At the highest olanzapine dose, mild akathisia was evident, along with a low rate of anticholinergic drug use to treat the motor side effects.

Other side effects of olanzapine include mild somnolence, dizziness, and weight gain. Weight gain can be substantial. Moreover, the appearance of abnormal carbohydrate metabolism, frank diabetes, and increases in plasma lipid measures have been noted and are being studied (Osser et al., 1999; Bettinger et al., 2000). Mild anticholinergic actions are evident, including dry mouth and constipation. No cardiac side effects have been noted with olanzapine, including tachycardia or electrocardiographic changes. No significant QTc prolongation occurs with this drug (Glassman and Bigger, 2001). In addition, no blood dyscrasias have been associated with olanzapine use, a side effect closely evaluated because of the structural similarity between olanzapine and clozapine. Transient dose-sensitive increases in hepatic transaminases have been noted, but these occur infrequently and reverse with continued treatment. Initial prolactin elevations were lower than with haloperidol and showed almost complete tolerance over time.

Quetiapine (Seroquel)
Although from a different chemical class, quetiapine displays many biochemical and behavioral similarities to clozapine. Quetiapine was developed by Zeneca Pharmaceuticals to have the low receptor affinity characteristics and many of the behavioral actions of clozapine. Quetiapine is the fourth antipsychotic marketed, and information on its clinical actions is still appearing.

Pharmacology
Quetiapine comes from the chemical class of dibenzothiazapine drugs. The drug binds to the D1, D5, D2, D3, D4, 5-HT2, 5-HT1A, α1, and α2 receptors, as does clozapine, but lacks clozapine-like affinity for the muscarinic cholinergic receptors. Its affinity to all of these receptors is low, similar to that of clozapine (Table 25.2). Quetiapine fails to up-regulate D2 dopamine receptors in striatum with chronic treatment. It increases dopamine metabolites in striatum as well as in nucleus accumbens with acute administration; it shows an acute but short-lived action on increasing plasma prolactin in rats. The anatomical selectivity of quetiapine in the depolarization block model is not yet clear (conflicting study findings have been reported). However, it shows selective action on regional c-fos activation, similar to that of clozapine, in that it fails to activate Fos pro-
teins in the dorsal striatum. Quetiapine inhibits conditional avoidance responding at high concentrations; it blocks dopamine agonist-induced behaviors in rats such as eye blink, climbing, and locomotor activity. Quetiapine induces catalepsy only at very high doses that are no longer clinically relevant (Saller and Salama, 1993). In neuroleptic-sensitized Cebus monkeys, quetiapine induces mild dystonias only in a high dose range, which is probably not clinically significant (Casey, 1996).

Metabolism and pharmacokinetics
Acute kinetics are linear; the drug shows good oral bioavailability. The elimination half-life ($T_{1/2}$) is approximately 6 hours. Plasma concentrations at steady state are linear up to a dose of 600 mg/day; for example, daily doses of 75, 300, and 600 mg produce steady-state (trough) plasma levels of 13.9, 43.9, and 91.1 ng/ml, respectively. Drug clearance is reduced in elderly schizophrenics, perhaps by 50%; therefore, in these patients, the dose should be reduced.

In vivo imaging
Preliminary imaging studies of quetiapine using $^{11}$C-RAC and PET show an occupancy in striatum at 2 hours of 44% and at 12 hours of 27% at the dopamine receptor. With $^{11}$C-NMSP, quetiapine shows an occupancy in cortex at the serotonin receptor at 2 hours of 72%, and at 24 hours of 50%. More recent imaging studies are consistent but show short-lived occupancy (Kapur et al., 2000).

Efficacy
Quetiapine demonstrates antipsychotic action significantly greater than that of placebo in several placebo-controlled trials at doses of 150–750 mg/day and action equivalent to that of haloperidol. Although this drug was initially recommended for use at 300 mg/day, many clinicians suspect that a much higher dose is optimal, closer to or above 750 mg/day. Therapeutic action on positive and negative symptoms of psychosis has been demonstrated, with the magnitude of its antipsychotic effect significantly greater than that of placebo in each domain and equivalent to that of haloperidol (Arvanitis and Miller, 1997). Additional efficacy data will no doubt appear and will be necessary to fully anticipate clinical action.

Side effects and safety
Routine safety parameters show a benign safety profile for quetiapine in all respects. Almost no motor side effects accompany its use; no episodes of extrapyramidal adverse events beyond placebo levels have been reported. No anticholinergic medication use beyond that of placebo has been necessary in any dose group. No akathisia is apparent. The most frequently observed side effects are sedation, somnolence, and headache. Significant weight gains occur, although less than with clozapine. Alterations in cholesterol metabolism are being studied. Transient and reversible increases in hepatic transaminase levels can be seen. No prolactin elevations are apparent in the 6–8 week parallel group studies comparing any dose group to placebo use. Although cataracts have been observed in some animal studies, and a warning to this effect previously appeared in labeling, no evidence to support this has been gathered in humans, and the warning has been removed. No significant QTc prolongion occurs with quetiapine (Glassman and Bigger, 2001).

NEW ANTIPSYCHOTICS: SELECTIVE DOPAMINE AND SEROTONIN RECEPTOR ANTAGONISTS
Some new antipsychotic drugs show effective antipsychotic action, with actions selectively at the dopamine and 5-HT$_{2A}$ serotonin receptors. Moreover, these drugs generally show evidence of greater serotonin than dopamine blockade, both pharmacologically and with occupancy studies.

Risperidone (Risperdol)
Soon after clozapine’s approval for use in the United States, risperidone was presented and reviewed in 1992 worldwide by Janssen. It was the first general-use antipsychotic reviewed by the U.S. Food and Drug Administration (FDA) in approximately 15 years. This long hiatus without new drug products for psychosis made the field and all consumers eager for this first new drug. Risperidone has been well received and widely prescribed for schizophrenia. Risperidone and clozapine have both been marketed for a sufficiently long time to allow head-to-head comparison trials with other new antipsychotics.

Pharmacology
Risperidone is a benzisoxazol derivative with high affinity for the 5-HT$_{2A}$ and D$_2$ receptors. Its in vitro affinity for 5-HT$_{2A}$ is 20 times higher than for D$_2$ receptors; its affinity for other serotonin receptor subtypes is lower by two or more orders of magnitude (Table 25.2). Risperidone has relatively high affinity for $\alpha_1$ noradrenergic and H$_1$ histamine receptors and moderate affinity for $\alpha_2$ sites. It lacks significant affinity for cholinergic receptors, for the sigma site, and for the D$_1$ receptor family. The major metabolite of risperi-
done, 9-hydroxy-risperidone, is active and has a receptor affinity profile similar to that of its parent compound (Leysen et al., 1994). Risperidone blocks both serotonin and dopamine agonist-induced behaviors in animal paradigms, with greater serotonergic than dopaminergic potency. It has no anticholinergic activity in behavioral or neurochemical tests. Risperidone increases dopamine turnover in frontal cortex and in the olfactory area but is less active in striatum (Fink-Jensen et al., 1996). It induces catalepsy in rats only at relatively high doses; but it induces dystonias in sensitized Cebus monkeys at clinically relevant concentrations (Casey, 1996). Risperidone has a similar effect on A9 and A10 dopamine neurons in the depolarization inactivation model, but its actions on both cell groups are atypical. At low dose levels, risperidone fails to stimulate c-fos expression in the dorsal striatum, whereas it activates the IEG briskly in the nucleus accumbens. Preclinically, the profile for anatomical selectivity is mixed and leaves questions about predictions for human motor side effects.

**Metabolism and pharmacokinetics**

Risperidone is metabolized by the liver isoenzyme CYP2D6. Its major metabolite is 9-hydroxyrisperidone (9-OHR), and it is pharmacologically active. Because the metabolite is renally excreted, both hepatic and renal metabolism is important to overall risperidone clearance. Individual genetic variation of the CYP2D6 isoenzyme and other concomitant 2D6-metabolized medications (e.g., fluoxetine) significantly alter drug clearance and plasma concentrations.

After a single 1 mg dose of risperidone, T\text{max} is 1 hour for risperidone and 3 hours for 9-OHR; T\text{1/2} for risperidone is 3.6 hours and for 9-OHR it is 22 hours. Kinetics are dose proportional up to 10 mg. In extensive metabolizers, T\text{1/2} is 2.8 hours, whereas for poor metabolizers it is 21.0 hours. The T\text{1/2} of 9-OHR remains 20–22 hours in both groups of metabolizers because its excretion is renally dependent. Also, in renally impaired individuals and in the elderly, overall risperidone metabolism and excretion are reduced (Ereshefsky and Lacombe, 1993).

**In vivo imaging**

With a 1 mg oral dose of risperidone, D\text{2} occupancy measured in striatum with \(^{11}\text{C}-\text{RAC} and PET was 50\% (range: 40\%–64\%). The 5-HT\text{2A} occupancy measured in cortex using \(^{11}\text{C}-\text{NMSP} with PET was 60\% (range: 45\%–68\%). Occupancy is dose proportional; thus, risperidone shows high occupancy with high doses (Kapur et al., 1999). Chronic risperidone treatment at low but clinically effective doses results in D\text{2} occupancy in striatum of less than 70\% (Nyberg et al., 1993).

**Efficacy**

Risperidone has been studied worldwide in actively psychotic patients with a diagnosis of schizophrenia. Its actions have been evaluated on positive and negative psychotic symptoms across a broad dose range (2–16 mg/day) in several large multicenter trials, with largely consistent findings. Risperidone treatment results in a significant reduction in positive and negative symptoms compared to placebo; positive symptoms respond to risperidone to a similar extent as haloperidol; the negative symptom response may be greater (Marder and Meibach, 1994). A risperidone dose of 3–6 mg/day seems to produce the best outcome of the doses tested, including its effects on positive and negative symptoms. These results are consistent across several risperidone efficacy studies, suggesting a U-shaped dose-response curve, with the greatest psychosis response occurring at a daily dose of 3–6 mg/day. Moreover, population survey data confirm physician use of lower doses of risperidone preferentially, with a good outcome (Love et al., 1999).

**Side effects and safety**

Motor side effects with risperidone are at placebo levels at doses below 6 mg/day. At doses above 10 mg/day, parkinsonism and akathisia are significant and probably similar to those with haloperidol. Anticholinergic drug use is also at placebo levels below 6 mg/day but progressively approaches the haloperidol use rate above 10 mg/day. Thus, below 6 mg/day of risperidone, parkinsonian motor side effects are minimal but rise thereafter. Agitation, anxiety, sedation, and insomnia have been reported with risperidone, but at rates similar to those of haloperidol. Hypotension was noted in normal volunteer studies but was not selectively noted in schizophrenic volunteers. The QTc is not affected by risperidone. Hyperprolactinemia is common, and frank galactorrhea can occur with risperidone. Mild weight gain occurs. However, alterations in carbohydrate or lipid metabolism have not been noted.

**Ziprasidone (Geodon)**

Ziprasidone was developed by Pfizer and is the fifth new antipsychotic to come to market. It was developed on the basis not only of its aminergic receptor binding profile (5-HT\text{2A} > DA\text{2}) but also its unique reuptake blockade property with the serotonin and noradrenergic reuptake proteins. This has encouraged the speculation that ziprasidone will treat schizophrenia with depression and/or anxiety, a question still not fully answered. The side effect profile of ziprasidone has received considerable attention: on the negative side, due to the QTc prolongation, and on the positive side, due
to the lack of any significant weight gain or alterations of cholesterol or lipid metabolism.

**Pharmacology**

The receptor binding profile of ziprasidone is distinctive in several respects. Its affinity for the D₂ family of receptors is high; 10-fold higher is its affinity for the 5-HT₂A receptor. Thus, the 5-HT₂A/DA ratio is very high and is the highest among the second-generation drugs. Moreover, it has significant affinity for several additional serotonin receptors, including 5-HT₁A, 5-HT₂C, and 5-HT₁D (Table 25.2). Ziprasidone is a partial agonist at the 5-HT₁A receptor and thereby increases extracellular dopamine levels in medial frontal cortex (Sharma and Shapiro, 1996; Daniel et al., 1999). It also acts as an antagonist at its other receptors. It is unique among the new antipsychotics in showing moderate affinity for and inhibition of the 5-HT and noradrenergic receptor proteins, comparable to the action of amitriptyline (Seeger et al., 1995). Moreover, it lacks significant affinity for the muscarinic M₁ receptor (Seeger et al., 1995).

Behaviorally, ziprasidone is a potent inhibitor of dopamine- and serotonin-mediated behaviors; it is six-fold more potent in inhibiting serotonergic than dopaminergic behaviors. It inhibits conditioned avoidance responding in rats. It decreases spontaneous locomotor activity and causes catalepsy, but the latter only at relatively high doses, thought to be no longer clinically relevant. Ziprasidone appears to affect equally dopamine cell firing in A9 and A10 neurons with chronic administration; therefore, it lacks the clozapine-like anatomical selectivity on dopaminergic function.

**Metabolism and pharmacokinetics**

Ziprasidone is metabolized by several hepatic and extrahepatic enzyme systems; hence, its plasma levels are relatively unaffected by other concomitant medications. In metabolic inhibition studies with ketoconazole, the CYP3A4 inhibitor of CYP3A4, ziprasidone plasma levels were unaffected. Safety is imparted by having multiple degratory drug routes. There appear to be no active metabolites of ziprasidone. The kinetics of ziprasidone are dose proportional at steady-state kinetics. At therapeutic doses, the $T_{\text{max}}$ is 4.7 ± 1.5 hours and the elimination half-life ($T_{1/2}$) is 10 hours.

**In vivo imaging**

Full assessment of ziprasidone occupancy at the D₂ receptor using PET (with $^{11}$C-RAC in striatum) and at the 5-HT₂ receptor (with $^{18}$F-septoperone in cortex) was carried out in normal human volunteers prior to patient studies to allow rational dose selection. Subjects received 40 mg of oral ziprasidone, and neurochemical scans were obtained at regular intervals over the next 36 hours, beginning at $T_{\text{max}}$. At 4 hours, $D₂$ occupancy in striatum was 79.4% and 5-HT occupancy in cortex was 98.5%. At 12 hours, $D₂$ occupancy was 52.8% and 5-HT₂ occupancy was 73.1%. Calculations from the model based on all the data predicted that at steady state with 40 mg ziprasidone administered bid, 5-HT₂ occupancy would remain at 90% and $D₂$ occupancy would average 75% (Bench et al., 1993, 1996).

**Efficacy**

Results from Phase II and III efficacy studies have been published. In these studies, ziprasidone was compared across a dose range of 40–160 mg/day to placebo and haloperidol at 15 mg/day. Ziprasidone demonstrated significant antipsychotic actions over the dose range of 80–160 mg/day (40–80 mg bid). Therapeutic action on positive symptoms was equivalent to that of haloperidol and comparable to that of other second-generation antipsychotics; significant antinegative effects occurred compared to those of placebo (O'Connor et al., 1997; Daniel et al., 2001). In patients with clinically significant depressive symptomatology at baseline, ziprasidone produced an antidepressant effect (Daniel et al., 2001).

**Side effects and safety**

Ziprasidone has been associated with a low rate of motor side effects at all of the doses tested, indistinguishable from placebo on SAS and BAS rating scales. The drug produced significantly lower levels of parkinsonism and akathisia than haloperidol. Moreover, anticholinergic drug prescriptions for motor side effects were at placebo levels (10%–15%) across the range of ziprasidone doses and were lower than with haloperidol at any dose (Daniel et al., 2001). Moreover, in contrast to several other new antipsychotics, ziprasidone causes no significant weight gain, either in the short term (Daniel et al., 2001) or in extended (12 month) trials. This advantage in avoiding weight gain is substantial relative to the other new antipsychotics in terms of cardiovascular health (Allison et al., 1999; Bettger et al., 2000) and compliance (Silverstone et al., 1988).

The most significant ziprasidone side effect is its mild but unequivocal effect on the QTc interval (Glassman and Bigger, 2001). In a rigorously conducted study to evaluate the extent of this drug side effect, the average QTc prolongation time with ziprasidone at peak plasma levels, at its highest recommended dose, was 20.3 ms (95% CI: 14.2–26.4), and this was not increased with a specific metabolic inhibitor (with ketoconazole: QTc = 20.0 ms; 95% CI: 13.7–26.2). Moreover, in its registration safety database of 7876 ECGs...
from 3095 patients, only 2 individuals had a QTc interval of over 500 ms (a lower rate than with placebo). Lastly, the all-cause mortality for ziprasidone in its registration safety database was 1.6 deaths per 100 patient treatment years, well within the range of 1.0–2.0 for all antipsychotics. Of additional and critical relevance is that ziprasidone has multiple routes of metabolic degradation, protecting against a drug-drug interaction increasing ziprasidone plasma levels. Ziprasidone is currently marketed with the warning that it not be used in individuals with preexisting heart disease. Ziprasidone use should not be restricted further than the FDA guidelines recommend, especially since its other effects and side effect advantages may be substantial.

**FUTURE ANTIPSYCHOTIC THERAPIES**

Not only are new antipsychotic drugs currently available, but the development pipelines of pharmaceutical houses and biotech companies remain full of potential antipsychotic drugs, some of which represent novel strategies. An appreciation is growing of the complexity associated with schizophrenia treatment and its diverse needs. Treatments for symptom constellations like cognitive dysfunction are being developed and tested (e.g., nicotinic agonists and D1 dopamine agonists), even if tentatively. Methodologies for assessment of new drugs, especially for diverse symptom constellations, are becoming increasingly sensitive and deliver considerable precision. Because the medical need in schizophrenia is high and because new drug actions have been successful, novel treatments with greater risks are being investigated. New treatment directions are being pursued based not only on successful hypotheses (e.g., the 5-HT2A > D2 affinity), but also on both moderately (e.g., D4 or D3 antagonists and partial dopamine agonists) and highly (e.g., indirect NMDA agonist or NR1 antagonist) speculative rationales (Lahti et al., 1996). These approaches will provide not only opportunities for novel therapeutic discovery, but also new knowledge about the pharmacology of psychosis in schizophrenia for pathophysiological consideration.

**TREATING THE SCHIZOPHRENIC PERSON**

Given these new groups of antipsychotic agents, the implications for schizophrenia therapeutics are broad. Treating physicians are likely to see their armamentarium of traditional antipsychotic compounds shift in the next few years from the first-generation to the second-generation antipsychotics. More drugs will be available to treat not only schizophrenics but also patients with other psychotic conditions, including psychotic persons with a poor drug response, children and adolescents, the elderly, and people with episodic or affective psychoses. Moreover, drugs selective for treating symptom domains within the diagnosis of schizophrenia (e.g., cognitive dysfunction) are likely to be developed. Motor side effects at present levels will hopefully become a complication of the past. This will happen none too quickly for the millions of schizophrenic persons who have had to trade a reduction in the symptoms of psychosis for the difficult motor side effects of traditional antipsychotics.

Optimal application of the new pharmaceuticals will require expanded knowledge not only of their clinical efficacy and safety, but also of their pharmacology, metabolism, pharmacokinetics, and in vivo behavior in brain. In addition, direct comparison of these compounds in the same clinical studies is now ongoing to define the selective superiority and comparative side effect profiles of the new antipsychotics. Much of these data were unavailable when traditional antipsychotics were characterized. This current expanded database for the new antipsychotics allows their administration and dosing with more precision and discrimination than was previously possible.

The practical considerations of deciding between new and traditional neuroleptics and among new neuroleptics in the clinical situation still need to be articulated. Recommended treatment algorithms already exist (American Psychiatric Association Workgroup on Schizophrenia, 1997). Economic advantage will always rest with the traditional drugs. Where efficacy is equivalent and motor side effects are minimal, traditional antipsychotics are adequate treatment choices. However, given the significant advantage of the new neuroleptics in reducing motor side effects, this characteristic may be paramount with respect to patient comfort, better medication compliance, and subsequent reduced psychosis relapse. Articulating principles to decide rationally among the new neuroleptics will require more clinical experience and data. The new drugs will probably differ in their motor side effect profile, cardiovascular actions, metabolism effects and weight gain, cognitive actions and side effects, negative symptom actions, and actions on depressive symptoms. All drugs have known kinetic profiles that may be decisive in a particular situation. However, direct comparative studies are necessary to provide a discriminatory clinical pharmacology for each compound.

Clozapine is probably being underutilized in the United States today. Larger numbers of neuroleptic-resistant psychotic patients exist than are being treated with clozapine. Factors including high cost and medical risk have no doubt diminished enthusiasm for this drug. Practical management techniques, such as increasing the clozapine dose slowly, transferring between drugs slowly, and treating benign side effects
symptomatically, will maximize clozapine’s effectiveness in individual persons. In responding patients, clozapine acts at a given dose within 12 weeks and at an average dose of 450 mg/day. Only 20% of treatment-refractory patients who are ultimately responsive to clozapine require doses higher than 600 mg/day to respond (Conley et al., 1997a). This information suggests fixed time and dose limits for broader clozapine testing in full and partial treatment-resistant schizophrenic persons. In an acute psychotic episode, the treating physician can choose between low-dose traditional or new drug treatment. The response to treatment in schizophrenia should be evaluated over many weeks. However, nonresponse to a regimen of traditional antipsychotic treatment even in early-break schizophrenic persons predicts subsequent nonresponse to other traditional antipsychotics in over 70% of persons. Thus, drug nonresponse can be characterized early in the illness.

This is a time of opportunity in schizophrenia treatment and research. We can anticipate that patient response and outcome will both improve. However, current treatments, even with the new antipsychotics, do not cure psychosis or schizophrenia. Full psychosis treatment will probably have to await a correct articulation of schizophrenia’s pathophysiology. This is an area where discovery could translate broadly into patient advantage.

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