The introduction of the first antipsychotic medication in the early 1950s revolutionized mental health care strategies and led to the era of deinstitutionalization, a period in which patients with schizophrenia and related psychotic disorders were released from state hospitals in large numbers to be cared for in the community (1). Nonetheless, with the growing understanding that a significant percentage of patients responds poorly to conventional antipsychotics, as well as the recognition of discouraging long-term outcomes for schizophrenia, the need to develop new therapeutic agents that work rapidly, potently, broadly, and with fewer side effects has become increasingly appreciated. The reintroduction of clozapine heralded the second generation of atypical antipsychotic drugs and a new pharmacotherapy of schizophrenia. To date, the greater benefits of the atypical antipsychotic drugs in many outcome domains have been demonstrated (2), and novel medications are replacing the conventional antipsychotics as treatments of choice. The development of additional novel strategies to obtain potentially new antipsychotic compounds possessing unique pharmacologic profiles with few side effects is being pursued based on specific hypotheses (3). This chapter provides a review and critique of currently available pharmacologic and psychosocial treatments in schizophrenia, and focuses on investigational treatments and potential strategies for future pharmacotherapy.

HISTORY OF ANTIPSYCHOTIC DRUG DEVELOPMENT

Since the discovery of the prototypical antipsychotic chlorpromazine in the early 1950s, a number of neuroleptics were developed based on the hypothesis that schizophrenia reflected a disorder of hyperdopaminergic activity, with the dopamine D2 receptor most strongly associated with antipsychotic response (4). In many patients with schizophrenia, the widely used conventional antipsychotic drugs (e.g., chlorpromazine and haloperidol) are effective in the treatment of the positive symptoms of schizophrenia, and also in preventing psychotic relapse (5); however, there are crucial limitations in the use of these agents. As many as 25% to 60% of patients treated with conventional antipsychotics remain symptomatic and are labeled either treatment-refractory, or partially responsive (3). In addition, these drugs at best only modestly improve negative symptoms of the deficit syndrome and a range of cognitive impairments, which may be fundamental to the disease (6). Further, conventional antipsychotics cause a variety of side effects both acutely (e.g., extrapyramidal side effects [EPS]) and with long-term exposure (e.g., tardive dyskinesia [TD]) (7,8). Such adverse effects may reduce compliance and represent a major drawback of these drugs.

For a number of years, there was a widely held view that any compound that was an effective antipsychotic agent must also induce EPS. The availability of clozapine and other newer atypical antipsychotic agents, however, have disproved this notion. The development of atypical antipsychotic drugs was aimed at increasing the ratio between doses that produce therapeutic effects and those that produce side effects, as well as improving efficacy (e.g., against a broader spectrum of psychopathologic symptoms and the treatment-resistant aspects of the disorder) (1). Although there is currently no uniform definition of the term “atypical,” in its broadest sense it is used to refer to drugs that have at least equal antipsychotic efficacy compared to conventional drugs, without producing EPS or prolactin elevation (1). A more restrictive definition would require that atypical drugs also have superior antipsychotic efficacy (i.e., they are effective in treatment resistant schizophrenic patients, and against negative symptoms and/or neurocognitive deficits).

Although agents like thioridazine were first suggested to
have atypical characteristics, it now is generally accepted that clozapine, first synthesized in 1958, is the prototypical “atypical” antipsychotic (9). Clozapine underwent extensive clinical testing in the 1970s, but its development was halted in the United States, and limited in other countries, because of a relatively high incidence of a potential fatal side effect, agranulocytosis. Nevertheless, its superior outcomes ultimately led to further development and eventual reintroduction beginning in 1990 (10). The renaissance of clozapine was based on several advantages: It appears to be more effective than typical neuroleptic drugs (e.g., chlorpromazine and haloperidol) in treatment refractory schizophrenia (11); it can ameliorate some of the negative as well as positive symptoms of schizophrenia (12); it can reduce relapse; it may improve certain cognitive functions; it may alleviate mood symptoms associated with schizophrenia and reduce the likelihood of suicidal behavior; it has very low liability for EPS and TD; and it does not induce sustained hyperprolactinemia (10). The reintroduction of clozapine represented a breakthrough in the treatment of schizophrenia. In recent years, concerted research and development efforts have been made to produce a second generation of “atypical” antipsychotic drugs, including risperidone, olanzapine, quetiapine, and ziprasidone, with the therapeutic advantages of clozapine, without the properties contributing to its serious side effects (13). Ongoing clinical evaluation of the new “atypical” antipsychotic drugs will eventually allow comprehensive assessment of their efficacy and safety.

**REVIEW AND CRITIQUE OF CURRENT SCHIZOPHRENIA PHARMACOTHERAPY**

**Conventional Antipsychotic Drugs**

**Pharmacology**

Conventional or typical antipsychotic drugs can be classified as high, intermediate, or low potency based on their affinity for dopamine D2 receptors and the average therapeutic dose, compared with a 100-mg dose of chlorpromazine (14). Haloperidol, the prototypical high-potency typical antipsychotic, has relatively high affinity for D2 receptors and a dose of 2 to 4 mg of haloperidol is equivalent to approximately 100 mg of chlorpromazine. Low-potency drugs (e.g., thioridazine) have a chlorpromazine equivalent dose of more than 40 mg. There is a good correlation between antipsychotic potency and D2 affinity for conventional antipsychotics of several chemical classes (4). Conventional drugs have various interactions with serotonin receptors, ranging from slight (e.g., haloperidol) to moderate (e.g., chlorpromazine).

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have further elucidated the importance of dopamine receptor occupancy as a predictor of antipsychotic response and adverse effects. Prospective studies have demonstrated that antipsychotic effects require a striatal D2 receptor occupancy of 65% to 70% (15–18), and D2 occupancy greater than 80% significantly increases the risk of EPS (15). Thus, a threshold between 65% and 80% D2 occupancy appears to represent the optimal therapeutic range to minimize the risk of EPS for typical antipsychotic drugs (18–20). It should be noted, however, that despite adequate D2 occupancy, many patients do not respond to medication (17). Moreover, results of studies with atypical drugs such as olanzapine indicate that receptor occupancy levels above 80% are not invariably associated with the occurrence of EPS, thus casting some doubt over the generalizability of the D2 occupancy model with regard to atypical antipsychotics (21).

In preclinical studies, acute treatment with conventional antipsychotics (e.g., haloperidol and fluphenazine) increases the expression of c-fos mRNA or Fos protein in the dorsolateral striatum, as well as the shell of nucleus accumbens in rats (22–25). Neuroleptic-induced expression of Fos in the nucleus accumbens has been postulated to relate to the antipsychotic activity of both conventional and atypical drugs (26,27). The Fos expression in the dorsolateral striatum, which is not induced by clozapine, has been proposed to be predictive of a liability to induce EPS (23,27). More recently, it has been reported that haloperidol, but not clozapine, increased the immediate-early gene, arc (activity-regulated cytoskeleton-associated gene) mRNA levels in the rat striatum (28). After chronic treatment, haloperidol also induces an increase in D2 receptor density and D21 receptor mRNA in the striatum (29–31). Interestingly, several investigators have reported striatal enlargement after chronic treatment with conventional antipsychotics, but not atypical drugs, in both schizophrenic patients (32,33) and rats (34). Thus, available data suggest that conventional antipsychotic drugs may induce long-term plastic changes that lead to morphologic alterations in the striatum, and that the efficacy and side-effect profile of typical antipsychotics relate to antagonistic actions at D2 dopamine receptors.

**Efficacy**

Although typical neuroleptics vary in side-effect profile and hence tolerability, there is little evidence for differences in efficacy between these drugs (3). However, in rare cases, patients failing a trial of one class may respond to the other. Although conventional neuroleptic drugs are effective for alleviating positive symptoms of schizophrenia, and preventing their recurrence in many patients, they have serious limitations. Approximately 30% of patients with acutely exacerbated psychotic symptoms have little or no response to conventional antipsychotics, and up to 50% of patients have only partial response to medication (5,7). Negative symptoms, mood symptoms, and cognitive deficits are marginally responsive to conventional neuroleptics. In particular, primary negative symptoms are very resistant to the
typical drugs (7,35). The presence of negative symptoms and cognitive impairment often leads to poor social and vocational function (36,37). Thus, in the absence of a clinical response at acute phase of the illness, clinicians often switch to a newer atypical agent (38).

**Safety**

Most conventional antipsychotics are associated with a wide range and a variable degree of undesirable acute and long-term adverse effects, including EPS; sedation; anticholinergic, autonomic, and cardiovascular effects; weight gain; sexual dysfunction; hyperprolactinemia; and neuroleptic malignant syndrome, a condition that is potentially life threatening (7,39). Up to 70% of patients given recommended therapeutic dosages of conventional antipsychotics develop acute EPS (40). The most troublesome neurologic side effect, tardive dyskinesia (TD), can be irreversible, and incidence rates have been estimated at about 5% per year in the nonelderly and as high as 30% per year in the elderly (41). Further, the anticholinergic drugs that are often used to reduce EPS, can also produce serious side effects (e.g., dry mouth, constipation, delirium and memory deficits) (42). All these adverse effects can contribute to treatment noncompliance, and hence increase rates of relapse and rehospitalization during the course of the chronic illness (7,39).

**Effectiveness**

Treatment with typical antipsychotics may result in poorer clinical and quality of life outcomes than with atypical antipsychotics (6). The mean first-year relapse rate during continuing maintenance treatment with conventional antipsychotics is approximately 26% in schizophrenic patients with first or multiple episodes (43). Even under the best conditions, when patients are maintained on therapeutic doses of depot conventional antipsychotics, approximately 30% of discharged patients with schizophrenia will be rehospitalized within 1 year (44). Hospital readmission rates are higher for conventional antipsychotics than for atypical antipsychotics (45). The monthly relapse rate of compliant patients taking optimal doses of a depot neuroleptic is estimated to be 3.5% per month, and the rate for patients who have discontinued their medication is 11.0% per month (44).

In terms of relapse prevention, higher doses of conventional antipsychotics may help stability, yet the patient’s quality of life will be reduced because of increased side effects. Often, when considering the best dose of a conventional antipsychotic, there is a trade-off between maximizing relapse prevention and optimizing comfort (46). Although there has been substantial progress in understanding maintenance dosing, for most patients with schizophrenia, this unfortunate trade-off is inevitable with conventional antipsychotic treatment (46).

**Atypical Antipsychotic Drugs**

A series of atypical compounds has been developed since the introduction of clozapine. These include risperidone, olanzapine, quetiapine, and ziprasidone, which were approved by the FDA in 2000, and aripiprazole and iloperidone, which are in late Phase III development.

**Pharmacology**

The pharmacologic properties that confer the unique therapeutic properties of atypical antipsychotic drugs are poorly understood despite intensive research efforts. Defining the role of the individual complex actions of clozapine responsible for its unique therapeutic profile (Table 56.1) is necessary for the rational design of new and improved atypical (clozapine-like) antipsychotics because this drug is the prototype atypical drug.

A distinguishing feature of clozapine in comparison to conventional antipsychotics is the relatively high affinity of clozapine for the 5-HT$_{2A}$ receptor. Meltzer and associates (47) provided evidence that combined 5-HT$_{2A}$/D$_2$ antagonistic actions, with greater relative potency at the 5-HT$_{2A}$ receptor, may be critical to atypicality, in terms of enhanced efficacy and reduced EPS liability. Based on this theoretic model, risperidone was developed to mimic the relative 5-HT$_{2A}$/D$_2$ affinities of clozapine, although risperidone has substantially higher affinity for both receptors than clozapine (Table 56.1). The reduced EPS side effects associated with low-dose risperidone treatment (4 to 6 mg per day), even at high levels of D$_2$ receptor occupancy, may be owing to the 5-HT$_{2A}$ antagonistic properties of the drug (47,48). However, at higher doses, risperidone produces EPS, indicating that 5-HT$_{2A}$ receptor antagonism alone cannot completely eliminate EPS associated with high D$_2$ receptor blockade. The potential role of 5-HT$_{2A}$ receptor antagonism in therapeutic responses to atypical antipsychotic drugs may become more apparent when data from clinical trials are available for the selective 5-HT$_{2A}$ antagonist M-100907. However, the results to date support the hypothesis that some degree of D$_2$ antagonism is still required to achieve antipsychotic effects. Moreover, at this point it is unclear what clinical effects 5-HT$_{2A}$ antagonism confers, in addition to mitigating the adverse effect of striatal D$_2$ antagonism, and propensity to cause EPS (21).

Risperidone, like clozapine, has relatively high affinity for $\alpha_1$- and $\alpha_2$-adrenergic receptors (Table 56.1), but the potential therapeutic significance of the adrenergic receptor blocking properties of clozapine and risperidone is uncertain. Addition of the $\alpha_2$-antagonist idazoxan to the regime of patients treated with the typical neuroleptic fluphenazine resulted in improved treatment responses in patients refrac-
neuronopharmacology: The Fifth Generation of Progress

Table 56.1. Affinity of Antipsychotic Drugs for Human Neurotransmitter Receptors (Ki, nM)*

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
<th>Aripiprazole</th>
<th>Iloperidone</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>290</td>
<td>580</td>
<td>52</td>
<td>1,300</td>
<td>130</td>
<td>410</td>
<td>320</td>
<td>120</td>
</tr>
<tr>
<td>D2</td>
<td>130</td>
<td>2.2</td>
<td>20</td>
<td>180</td>
<td>3.1</td>
<td>0.52</td>
<td>6.3</td>
<td>1.4</td>
</tr>
<tr>
<td>D3</td>
<td>240</td>
<td>9.6</td>
<td>50</td>
<td>940</td>
<td>7.2</td>
<td>9.1</td>
<td>7.1</td>
<td>2.5</td>
</tr>
<tr>
<td>D4</td>
<td>47</td>
<td>8.5</td>
<td>50</td>
<td>2,200</td>
<td>32</td>
<td>260</td>
<td>25</td>
<td>3.3</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>140</td>
<td>210</td>
<td>2,100</td>
<td>230</td>
<td>2.5</td>
<td>93</td>
<td>93</td>
<td>3,600</td>
</tr>
<tr>
<td>5-HT1D</td>
<td>1,700</td>
<td>170</td>
<td>530</td>
<td>&gt;5,100</td>
<td>2</td>
<td>&gt;5,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT2A</td>
<td>8.9</td>
<td>0.29</td>
<td>3.3</td>
<td>220</td>
<td>0.39</td>
<td>20</td>
<td>5.6</td>
<td>120</td>
</tr>
<tr>
<td>5-HT2C</td>
<td>17</td>
<td>10</td>
<td>10</td>
<td>1,400</td>
<td>0.72</td>
<td>43</td>
<td>43</td>
<td>4,700</td>
</tr>
<tr>
<td>5-HT6</td>
<td>11</td>
<td>2,000</td>
<td>10</td>
<td>4,100</td>
<td>76</td>
<td>160</td>
<td>63</td>
<td>6,000</td>
</tr>
<tr>
<td>5-HT7</td>
<td>66</td>
<td>3</td>
<td>250</td>
<td>1,800</td>
<td>9.3</td>
<td>15</td>
<td>110</td>
<td>1,100</td>
</tr>
<tr>
<td>α1</td>
<td>4</td>
<td>1.4</td>
<td>54</td>
<td>15</td>
<td>13</td>
<td>57</td>
<td>1.4</td>
<td>4.7</td>
</tr>
<tr>
<td>α2</td>
<td>33</td>
<td>5.1</td>
<td>170</td>
<td>1,000</td>
<td>310</td>
<td>160</td>
<td>160</td>
<td>1,200</td>
</tr>
<tr>
<td>H1</td>
<td>1.8</td>
<td>19</td>
<td>2.8</td>
<td>8.7</td>
<td>47</td>
<td>470</td>
<td>470</td>
<td>440</td>
</tr>
<tr>
<td>m1</td>
<td>1.8</td>
<td>2,800</td>
<td>4.7</td>
<td>100</td>
<td>5,100</td>
<td></td>
<td></td>
<td>1,600</td>
</tr>
</tbody>
</table>

*Values are geometric means of at least three determinations.


ency clozapine, the two drugs have many common receptor binding characteristics. Primary considerations in selection of olanzapine for development were the drug’s relatively potent antagonistic effects at both D2 and 5-HT2A receptors (51,52). Olanzapine is more potent at 5-HT2A than D2 receptors (Table 56.1), similar to clozapine and risperidone. In addition, receptor binding characteristics of olanzapine in regard to other dopaminergic, serotonergic, cholinergic, and adrenergic receptor subtypes are similar to clozapine, but there are also some notable distinctions between the two drugs. For example, clozapine has substantially higher affinity for 5-HT1A and 5-HT7 receptors in comparison to olanzapine (Table 56.1).

Quetiapine is another drug with greater relative affinity for 5-HT2A than for D2 receptors, but also some affinity for α1-adrenergic and H1 receptors (53) (Table 56.1). Interestingly, quetiapine produces only transiently high striatal D2 occupancy in schizophrenic patients, although the study has clinical and technical limitations (54). Ziprasidone has potent 5-HT2A and D2 affinities, and like clozapine, it shows 5-HT1A agonist properties that could potentially act as protective effects on the development of EPS. Ziprasidone also has significant affinity for 5-HT1D and 5-HT2C, as well as H1 and α1-adrenergic receptors (55) (Table 56.1). Iloperidone has in addition to affinity for 5-HT2A and 1A and D2,3 receptors, also affinity for the α1- and α2c-adrenergic receptors. Aripiprazole is distinct from the other atypical antipsychotic drugs because it is selective for the dopamine system and acts through partial agonism.

PET studies showing that therapeutic doses of risperidone and olanzapine produce greater than 70% occupancy of D2 receptors suggest that D2 receptor antagonism could be a predominant mechanism of action of these atypical drugs (56,57). Clozapine, however, does not exhibit high levels of D2 receptor occupancy at therapeutically effective dose (15,57,58), suggesting that D2 receptor antagonism alone cannot explain the greater therapeutic efficacy of clozapine (13). The low occupancy of striatal D2 receptors by clozapine could account for its low EPS liability (20,58,59).

Clopazpine, risperidone, and olanzapine occupy more than 80% of 5-HT2A receptors in the therapeutic dose range in humans (15,56–58,60). Although 5-HT2A receptor antagonism is likely to be associated with the low EPS liability of risperidone and olanzapine, the role of this molecular action in the superior therapeutic responses to clozapine is unclear (13).

Efficacy

Although the proportion of patients who improve and the magnitude of therapeutic effects vary greatly, atypical anti-
psychotics are at least as effective for psychotic symptoms as conventional drugs (3). Well-controlled double-blind studies of atypical antipsychotics suggest that clozapine, risperidone, and olanzapine may be superior to haloperidol for controlling psychotic symptoms (61). At selected doses, risperidone appears to be more effective than haloperidol in treating positive and negative symptoms (53). Olanzapine has been demonstrated to be effective for positive, negative, and depressive symptoms (62), and in some studies the drug was superior to haloperidol and risperidone in terms of negative symptoms and long-term efficacy (63,64).

However, in a recent large double-blind study (that has only been preliminarily reported), risperidone demonstrated significantly greater efficacy than olanzapine in reducing anxiety/depression and positive symptoms (65). Quetiapine appears to be comparable to chlorpromazine and haloperidol in treating both positive and secondary negative symptoms (61). Similarly, ziprasidone appears to be as effective as haloperidol in alleviating positive and negative signs in an acute treatment study (66), whereas a 52-week placebo-controlled maintenance study found primary and secondary negative symptom efficacy for ziprasidone (67).

Table 56.2. Clinical and Side-Effect Profile of Atypical Antipsychotic Drugs

<table>
<thead>
<tr>
<th></th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>+++</td>
<td>+++?</td>
<td>+++?</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>+++</td>
<td>++</td>
<td>+++?</td>
<td>++?</td>
<td>+?</td>
</tr>
<tr>
<td>Refractory symptoms</td>
<td>+++</td>
<td>+++?</td>
<td>+++?</td>
<td>+?</td>
<td>+?</td>
</tr>
<tr>
<td><strong>Side effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPS</td>
<td>—</td>
<td>++</td>
<td>++</td>
<td>—</td>
<td>+a</td>
</tr>
<tr>
<td>TD</td>
<td>—</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Prolactin elevation</td>
<td>—</td>
<td>+++</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Dose dependent. EPS, extrapyramidal side effects; TD, tardive dyskinesia; + to ++++, weakly (for clinical effect) or active (for side effect) to strongly active; – to —, weak to little activity; ?, questionable to unknown activity.

that the atypical drugs are unable to fully reverse already-established impairment in cognition, negative symptoms, and social disability in many patients (79). Thus, the possible use of these agents in the prodromal period of schizophrenia, before the emergence of psychosis, is an important issue to address in the next decade (79).

Safety

Although atypical antipsychotics were developed to improve on the shortcomings of conventional drugs it has already become apparent that they also have significant limitations in terms of side effects in the relatively brief period that they have been in general clinical use (3). As a class, and with some variation between the individual drugs (Table 56.2), they have a much more favorable side-effect profile, particularly in terms of EPS and TD. They do, however, produce side effects, including sedation, hypotension, dry mouth, constipation, sedation, and some types of sexual dysfunction (3). Neuroleptic malignant syndrome has also been reported with atypical antipsychotics such as clozapine, risperidone, and olanzapine (80). Weight gain is the most worrisome and potentially serious side effect that appears to be class wide, except perhaps for ziprasidone and drugs that have not yet been approved for marketing by the FDA, including aripiprazole and iloperidone (81). In particular, weight gain and sedation are common reasons for drug discontinuation for adolescent patients (78). In addition, the atypical antipsychotics have been associated with new onset type II diabetes mellitus (82). It is unclear whether these effects are secondary to weight gain, independent, or causative. Atypical drugs are also associated with increases in cholesterol and lipids, the long-term medical consequences of which are largely unknown (78). It appears prudent to monitor fasting blood sugar and lipid levels in patients treated with these agents. The new atypical drugs also have their own individual and idiosyncratic side-effect profiles (Table 56.2). Thus, each new drug should be evaluated individually in terms of side effects and safety (39).

Clozapine is associated with a very low propensity for EPS and little or no incidence of TD; thus, it is a valuable option for patients who experience EPS (11). However, clozapine can cause serious side effects that impose substantial limitations on its use. Not only must initial dose titration be quite gradual, but also there is a significant occurrence (around 0.9%) of agranulocytosis (83) and seizures, as well as sedation, hypotension, hypersalivation, and weight gain (8). The frequency of agranulocytosis with clozapine is such that regular white blood count monitoring is required (8).

Risperidone has a favorable side effect profile in comparison to haloperidol (84). Risperidone can produce dose-related EPS (≥6 mg per day), but the rate of TD is low (0.6%) for dose currently used (2 to 8 mg per day) (84, 85). Risperidone is associated with prolactin elevation, hypotension, somnolence, insomnia, and agitation (39,86). The incidence of EPS with olanzapine is not significantly different from that with placebo, and the incidence of olanzapine-related TD is low (1%) (87). There is a risk of mild sedation and mild anticholinergic side effects, and the risk of weight gain appears greater than with risperidone, but comparable to clozapine (78).

Quetiapine is associated with very low levels of EPS and its prolactin level elevation is indistinguishable from that of placebo (88). The incidence of TD with quetiapine is reportedly low or virtually nonexistent, although this remains to be demonstrated prospectively. There is a potential risk of lenticular opacities that were associated in one preclinical study in beagles (89), but have not been found in nonhuman primates or patients, yet monitoring is recommended until additional data are available. The risk of weight gain with quetiapine appears to be less than that with olanzapine and clozapine (78). Although quetiapine has virtually no cholinergic activity, tachycardia is a possible side effect, perhaps secondary to its adrenergic effects on blood pressure (39). There are several other side effects with quetiapine such as decrease in T3 and T4, orthostatic hypotension, and sedation, necessitating gradual dose titration (39).

Ziprasidone has a risk of EPS that is not significantly different from that with placebo (90). The risk of TD is not known. Ziprasidone is associated with mild dyspepsia, nausea, dizziness, and transient somnolence (90). Ziprasidone treatment has been associated with minimal weight gain, which could distinguish it among other atypical agents (80). The FDA delayed ziprasidone approval because of concern about its ability to prolong the Q-T interval (90), but an FDA Advisory Committee recommended its approval for the treatment of schizophrenia in July 2000, and the FDA issued an approval letter in September 2000.

Effectiveness

Considerable evidence indicates that relapse and rehospitalized rates are substantially better with the group of atypical antipsychotics than with conventional antipsychotics for patients who are compliant with their maintenance antipsychotic regimen (46). The decreased EPS liability of the atypical drugs will make it easier to prescribe more effective doses of antipsychotic that can maximize relapse prevention, without simultaneously interfering with the patient’s quality of life or motor functioning (46). Patient-based measures of quality of life show improvement with the atypical drugs over the conventional neuroleptics (45).

In one randomized controlled trial comparing clozapine with standard neuroleptic therapy for treatment-resistant schizophrenic inpatients, the actual hospital discharge rates at 1 year were 27% for clozapine and 29% for standard care (91). The clozapine group, however, had decreased readmission rates within the first 6 months compared with the neuroleptic group (3% versus 29%) (91).
In another randomized double-blind comparative study of clozapine and haloperidol in patients with refractory schizophrenia over 1 year, clozapine-treated patients showed significant quality-of-life improvements when compared with haloperidol-treated patients (53% versus 37%) (92). The patients assigned to clozapine had significantly fewer mean days of hospitalization for psychiatric reasons than patients assigned to haloperidol (144 versus 168 days) and used more outpatient services (134 versus 98 units of service) (92).

Several studies have examined the impact of risperidone on health care utilization in the 2 years before and after risperidone treatment in small groups of schizophrenic patients. Decreases of 20% to 31% in the number of hospitalization days were reported (93,94), but Viale and colleagues (95) observed an increase of 12% in hospitalization days in the first year of risperidone therapy.

Extensive controlled studies have proven olanzapine to be significantly superior to haloperidol in long-term maintenance of response (62,96). The estimated 1-year risk of relapse was 19.7% with olanzapine and 28% with haloperidol (97). Furthermore, a significantly greater proportion of the olanzapine- than risperidone-treated responders maintained their improvement in the extended follow-up after 28 weeks of therapy (63). It is not clear whether the lower relapse rates are owing to increased prophylactic efficacy or better treatment compliance because of better tolerability. To date, there have been no definitive prospective random-assignment studies on compliance rates for atypical antipsychotics (46).

Cost-Effectiveness in Comparison with Conventional Drugs

Atypical antipsychotic drugs are approximately 10 to 40 times more expensive than conventional drugs (98). In the past few years, a number of studies comparing the cost-effectiveness of the atypical antipsychotics with that of the typical drugs have been published. However, many of these studies have frequently been criticized because of limitations in experimental design; thus, the cost-effectiveness of atypical antipsychotics has not yet been fully established (98, 99). Most of the available cost-effectiveness evidence is from retrospective studies or economic computer models, which have considerable methodologic limitations (98).

Perhaps the best study of the cost-effectiveness of clozapine published to date in terms of its methodology is a randomized controlled trial conducted by Rosenheck and associates (92), that compared clozapine with haloperidol in patients with treatment-refractory schizophrenia over 1 year. After 1 year of treatment, the clozapine group had lower inpatient but higher outpatient costs. The total medical costs (including inpatient hospital costs, outpatient medical costs, and medication costs) of the clozapine group ($58,000) were not significantly lower than the haloperidol group ($61,000). Overall, clozapine was concluded to be cost neutral, although it demonstrated improved clinical outcomes, suggesting that it may be cost-effective (92).

The higher price of olanzapine compared with classic neuroleptics may be offset by reductions in the use of inpatient and outpatient services (45,100). For example, Hamilton and colleagues (100) compared the cost-effectiveness of olanzapine to those of haloperidol for the treatment of schizophrenia, in a randomized clinical trial, for 6 weeks (acute phase) and up to 1 year (maintenance phase). The medication costs for olanzapine were about 22 times larger than those for haloperidol after 6 weeks of treatment; however, patients treated with olanzapine had significantly lower inpatient and outpatient medical expenses than patients treated with haloperidol. Overall, mean total medical costs during the acute phase for the olanzapine patients were significantly lower (US$388/6 weeks) than those for the haloperidol patients. As was seen in the acute phase, these total medical cost differences were sustained (US$636 lower per patient for olanzapine over 46 weeks) during the maintenance phase (100). Glazer and Johnstone (99) also reported that the total health care costs for olanzapine treatment for 6 weeks and up to 1 year were lower than those for haloperidol treatment ($431/month lower and $345/month lower, respectively).

Palmer and associates (101) used a decision analytic model to estimate the total medical costs and effectiveness outcomes of olanzapine, haloperidol, and risperidone over 5 years for schizophrenia treatment in the United States. The estimated 5-year total medical cost of olanzapine, haloperidol, and risperidone was US$92,593, $94,132, and $94,468, respectively. The estimated disability-free years of these agents were 3.19 (olanzapine), 2.62 (haloperidol), and 3.15 (risperidone). The quality-adjusted life years (QALYs) were 3.15 (olanzapine), 2.95 (haloperidol), and 3.12 (risperidone). These data suggest a modest cost-effectiveness advantage for olanzapine over haloperidol and risperidone (101), whereas the decision-modeling approach appears to be subjective to imprecision and possible bias (45). There have been no published randomized controlled studies of the cost-effectiveness of risperidone. In addition, so far, no prospective randomized studies have been completed that compare the cost-effectiveness of the atypical antipsychotics to each other for the treatment of schizophrenia. Furthermore, the other atypical drugs are too new to have had their cost-effectiveness evaluated to any significant extent. Additional prospective randomized clinical trials with larger sample sizes and long-term assessment should be conducted in order to evaluate the cost-effectiveness of atypical antipsychotics adequately (45).

First-Episode Patients

Pharmacotherapy

First-episode patients as a group may differ from chronic patients in several aspects of pharmacologic responsiveness.
Relatively high response rates of positive and negative symptoms have been reported in first-episode samples; for example, Lieberman and colleagues (102) reported remission rates of 83% after 1 year of treatment with conventional antipsychotic agents in 70 first-episode patients. Surprisingly, remission did not occur until a median of 11 and mean of 36 weeks of treatment. Despite the apparent heightened responsiveness of first-episode patients, residual cognitive deficits and poor psychosocial adjustment are common (103,104). First-episode patients may also require a lower mean dose of antipsychotic medication and may be more sensitive to drug side effects compared to more chronic patients (105). Kopala and colleagues (106) treated 22 first-episode patients openly with risperidone for a mean of 7 weeks and observed a 91% response rate in patients who received risperidone 2 to 4 mg per day compared to a 27% response rate in patients who received a dose of 5 to 8 mg per day. The lower-dose group exhibited no EPS, whereas 32% of the higher-dose group developed akathisia or parkinsonism. However, because this was not a fixed-dose design, conclusions regarding dose–response relationships must be considered preliminary. In a different approach, Sanger and colleagues (107) analyzed results from the 83 first-episode patients (out of a total of 1,996 subjects) who participated in a double-blind, 6-week comparison of olanzapine and haloperidol. First-episode patients who received olanzapine had significantly better clinical response and fewer EPS than the haloperidol group. Of particular interest, first-episode patients treated with olanzapine achieved a significantly higher response rate than chronic patients treated with haloperidol. In addition, chronic patients treated with haloperidol developed significantly fewer EPS than first-episode patients treated with haloperidol. Mean doses of haloperidol and olanzapine were similar between first-episode and chronic patient groups (10.8 versus 11.0 mg per day and 11.6 versus 12.0 mg per day, respectively). Although these findings suggest that the relative benefits of olanzapine (and perhaps of other atypical agents) compared to conventional agents may be greater in first-episode patients than chronic patients, issues of nonequivalent dosing between drugs may be of particular concern in light of recent work indicating that optimal D2 receptor blockade may be achieved in first-episode patients with haloperidol 0.25 to 2 mg per day (18). Two other double-blind controlled studies have been preliminarily reported that address the question of whether first-episode patients respond better to atypical antipsychotic drugs. The first is a 52-week study of clozapine versus chlorpromazine in 164 first-episode treatment naive schizophrenia patients in China (108). The cumulative response rates of patients at 12 and 52 weeks, respectively, were 81.2% and 96.3% for clozapine (mean dose 292 mg per day), and 68.3% and 97.7% for chlorpromazine (mean dose 319 mg per day). The first-episode patients treated with clozapine had more rapid response, fewer EPS, and higher treatment retention and relapse prevention than the chlorpromazine group (108). The second is a comparison between olanzapine and haloperidol in 262 patients with first-episode psychotic disorder (109). At 12 weeks, the patients treated with olanzapine (mean dose 9.1 mg per day) demonstrated a higher response rate (55% versus 46%) and greater cognitive improvement than the patients treated with haloperidol (mean dose 4.4 mg per day).

Response of first-episode patients has also received renewed attention because of the widely held belief that early intervention may favorably affect the course of the illness. This hypothesis, which often invokes “neurotoxicity of untreated psychosis” as a mechanism, is largely based on one naturalistic study reported by Loebel and colleagues (110). Other naturalistic studies have failed to find a relationship between duration of initial untreated illness and outcome (111–113). Prospective controlled trials are needed to determine whether early intervention with specific antipsychotic agents improves the early course of the illness.

**Psychosocial Interventions**

Psychosocial interventions potentially may have the greatest impact on first-episode patients and their families. Preliminary studies have looked at stress-reduction approaches for patients identified as “premorbid” or at risk for schizophrenia, combining cognitive therapy or stress reduction interventions alone or in combination with medication (114–116). Preliminary studies have indicated that cognitive-behavioral therapy (CBT) approaches that have been developed for patients with treatment-resistant psychosis can be successfully modified for first-episode patients (117). Psychoeducation, family support, and interventions to enhance compliance are also expected to play important roles early in the course of the illness. However, two studies of first-episode patients in Norway failed to find benefit from the addition of behavioral family management (BFM), which emphasizes communications skills, to a basic psychoeducation program (118,119). The authors concluded that families of first-episode patients may be in greatest need of information and support, rather than the intensive communication skills training offered by BFM.

**Maintenance Treatment**

**Pharmacotherapy**

Maintenance treatment with conventional and atypical antipsychotic medications has consistently demonstrated prophylactic efficacy against relapse. Hogarty (120) reviewed the literature on maintenance treatment with conventional antipsychotic agents and found that the average relapse rate during the first year after hospitalization was 41% with active medication compared to 68% with placebo. Among patients who survived the first year, annual relapse rates with medication dropped to 15%, whereas relapse rates on
placebo remained constant at 65%. This pattern suggests that maintenance treatment is relatively ineffective for a substantial proportion of patients; only after this poorly responsive subgroup is removed from the sample does the benefit of medication become fully apparent. Consistent with this view are the results of a low-dose maintenance treatment trial with depot fluphenazine in which a dose–response relationship only emerged during the second year of follow-up (121,122). Depot preparations have significantly lowered relapse rates by an average of 15% compared to oral neuroleptics in six double-blind, randomized trials (123). The advantage of depot administration may be understated in these trials, however, because research subjects were probably poorly representative of typical clinical samples and most trials did not extend beyond 1 year. Research comparing low and standard-dose maintenance with depot neuroleptics has demonstrated a trade-off between adverse effects with higher doses, including neurologic side effects and dysphoria, versus increased relapse rates with lower doses (122, 124). “Intermittent” maintenance treatment was associated with an unacceptable rate of hospitalizations, whereas relapses associated with low-dose depot medication generally were responsive to rescue with brief augmentation with oral neuroleptic or benzodiazepine; hospitalization rates were not elevated with low compared to standard doses (122, 124). Carpenter and colleagues (125) reported that administration of diazepam at the earliest sign of exacerbation in medication-free patients was more effective than placebo and comparable to fluphenazine in preventing relapse. This work suggests that lower doses of depot neuroleptic may provide acceptable protection against relapse if accompanied by close monitoring and rapid psychosocial and pharmacologic intervention at the first sign of relapse. These measures presumably will also enhance maintenance treatment with atypical agents, although dose-limiting side effects are not as problematic.

Growing evidence suggests that maintenance treatment with atypical agents provides greater protection against relapse compared to conventional oral agents. In a large, open trial, Essock and colleagues (126) found that chronically hospitalized patients randomized to clozapine were not more likely to be discharged than patients receiving treatment as usual, but once discharged, relapse rates were significantly lower with clozapine. Pooled results from three double-blind extension studies revealed that relapse rates were significantly lower with olanzapine (20%) compared to haloperidol (28%) in patients with schizophrenia and related psychoses (97). Until depot preparations of atypical agents are available for study, it will be difficult to determine whether the advantage of certain atypical agents is primarily the result of enhanced compliance versus a direct modulatory effect on symptom exacerbation. It is clear from depot neuroleptic studies that large numbers of patients relapse despite adequate compliance; relapse in medication-compliant patients is often associated with depression and resolves spontaneously without change in medication (127). Whether all atypical agents are equally effective in preventing relapse is also unknown. In a naturalistic study, Conley and colleagues (128) found that relapse rates were quite similar during the first year after discharge in patients treated with clozapine versus risperidone. During the second year, no additional relapses occurred on clozapine, whereas the rate of relapse on risperidone increased from roughly 13% to 34%. In the only published comparison between risperidone and olanzapine, rates of exacerbation (increase in PANSS score by 20%) were significantly higher at 28 weeks in patients who had responded to risperidone (mean dose 7 mg per day) compared to olanzapine (mean dose 17 mg per day) (63). It will be important to determine whether specific drugs differ in prophylactic efficacy against relapse when compliance is controlled and issues of dosing equivalence are addressed. It is possible that clozapine and perhaps other atypical agents are more effective in suppressing relapse; this effect may be relatively independent of antipsychotic efficacy and mediated by different neurotransmitter systems. Continued development of psychosocial interventions to improve compliance and monitor and respond to early signs of relapse will be equally important.

**Psychosocial Interventions**

A diverse range of psychosocial interventions has been shown to reduce relapse rates. In over 20 controlled trials, family therapies emphasizing psychoeducation and support have reduced relapse rates for schizophrenia patients who have regular contact with family members (129,130). Although differences in theoretical orientations and intensity of treatment have not produced consistent differences in efficacy, recent evidence has suggested that multiple-family psychoeducation groups may be particularly effective (131). Several controlled trials have also indicated that relapse rates can be reduced by assertive community treatment programs (PACT) or similar outreach programs that provide intensive monitoring, skills training, and case management in the community, usually with continuous availability of staff (132,133). Social skills training improves role functioning of patients with schizophrenia, but has not substantially reduced symptoms or reduced relapse rates compared to control conditions in most studies (134). In an illuminating study, Herz and colleagues (135) found that a relatively simple, weekly monitoring of schizophrenia patients in psychoeducation groups in conjunction with the availability of rapid pharmacologic and psychosocial interventions at the first sign of decompensation substantially reduced relapse rates, by approximately fourfold, compared to treatment as usual.

**Noncompliance**

**Pharmacotherapy**

Cramer and Rosenheck (136) surveyed the literature on antipsychotic medication and found that compliance rates
towards medication and discharge planning during acute motivational interviewing techniques that target attitudes and therapy,” a four- to six-session intervention based on motivational interviewing techniques that targets attitudes towards medication and discharge planning during acute hospitalizations. In a randomized, controlled trial, compliance therapy was found to improve insight and observed adherence to treatment over an 18-month treatment period (147). Patients in the compliance therapy group also displayed significantly greater improvement in social functioning and lower relapse rates than the control group (147). In addition to educational and skills training approaches, Cramer and Rosenheck (148) demonstrated that interventions that assist patients in remembering to take medications, such as placing microchip schedulers on pill bottles, can also substantially improve compliance.

Treatment Resistance

Estimates of the incidence of treatment resistance have varied with changes in the diagnostic classification of schizophrenia and definitions of treatment response (149), which have tended to obscure potential improvements in outcome associated with advances in pharmacologic and psychosocial treatments. For example, Hegarty and colleagues (150) reviewed results of 320 clinical trials and found that, since the introduction of modern antipsychotics in the mid-twentieth century, about 50% of patients were improved at follow-up, whereas the rate of improvement dropped to 35% in the decade ending in 1994. A narrowing of the diagnostic criteria is believed to account for this decline in response rates. Rates of response have tended to be higher in first-episode psychosis, although dropout rates have been high in this population, particularly with conventional agents (102,107). Persistence of psychotic symptoms is more common in drug trials involving chronic patients, presumably reflecting progression of the illness as well as a possible selection bias favoring participation by more refractory patients. If the definition of treatment resistance is broadened to include persistence of negative symptoms, cognitive deficits, or failure to achieve premorbid levels of functioning, treatment resistance can be considered the rule rather than the exception.

Psychotic Symptoms

Antipsychotic Monotherapy

Response of psychotic symptoms to conventional antipsychotics, risperidone, and olanzapine has been associated with D2 receptor occupancy in excess of 65% (18,57), although persistence of psychotic symptoms has been shown to occur despite adequate D2 blockade in a subgroup of refractory patients (151). As noted, only clozapine has consistently demonstrated efficacy for psychotic symptoms in treatment of refractory patients; the mechanism responsible for this therapeutic advantage remains uncertain. In a sample of 268 patients prospectively established to be neuroleptic resistant, 30% in the clozapine group met criteria for response at 6 weeks compared to 7% treated with chlorpromazine (11). Response rates as high as 60% have been re-

Psychosocial Interventions

Most approaches to noncompliance involve psychoeducation, supervision, and supportive therapy in which the benefits of treatment are emphasized, whereas barriers to adherence and medication side effects are minimized (145). Family therapy and social skills training may also exert a positive impact on compliance. Cognitive behavioral approaches have recently been applied to noncompliance by Kemp and colleagues (146,147), who developed “compliance therapy,” a four- to six-session intervention based on
ported after 6 months in open trials with clozapine in patients less rigorously defined as treatment refractory (152). The extent to which a prolonged trial is necessary to determine efficacy of clozapine and other atypical agents is the subject of debate (153,154).

The relative efficacy of atypical agents other than clozapine in patients who have failed conventional neuroleptic therapy is less clear. Marder and colleagues (155) found that schizophrenia patients presumed to be treatment-resistant on the basis of having been hospitalized for 6 months or longer at the time of study entry did not respond to haloperidol 20 mg per day but significantly improved with risperidone 6 mg per day or 16 mg per day compared to placebo. Similarly, analysis of a subgroup of 526 patients from a larger trial identified retrospectively as having had a poor response to at least one prior antipsychotic, revealed greater response of psychotic symptoms to olanzapine (mean dose 11 mg per day) than haloperidol (mean dose 10 mg per day); this difference was significant in the intent-to-treat analysis but not in a comparison of completers (76). Trials specifically designed to study treatment-resistant patients have provided less consistent support for efficacy of risperidone and olanzapine. In 67 schizophrenia patients with histories of neuroleptic resistance, risperidone 6 mg per day significantly improved total BPRS scores compared to haloperidol 15 mg per day at 4 weeks, but response did not differ between groups at 8 weeks (156). In contrast, risperidone produced significantly higher response rates than haloperidol in a large, randomized open trial involving 184 schizophrenia patients with a history of poor response (157). Relative response of psychotic symptoms to risperidone increased over time and reached a maximum improvement compared to haloperidol at the final 12-month assessment. In a 6-week trial designed to mirror the landmark Clozapine Collaborative Trial (11), only 7% of patients prospectively determined to be treatment resistant to haloperidol responded to olanzapine 25 mg per day, a response rate that did not differ from chlorpromazine (77). The same group reported that 41% of 44 patients identified as unresponsive to olanzapine in the preceding study or in an open trial subsequently exhibited a response to clozapine (158). In addition, open trials in which patients have been switched from clozapine to olanzapine or risperidone have reported a high incidence of clinical deterioration, casting doubt on claims for therapeutically equivalent between clozapine and the second-generation agents, at least at the doses tested (159,160). Of interest, two controlled trials have found comparable efficacy for risperidone and clozapine. However, in one 4-week trial, the 59 participants were not screened for treatment resistance at baseline and, despite equivalence in outcomes between groups using an LOCF analysis, 25% of the risperidone group dropped out owing to lack of efficacy compared to only 5% in the clozapine group (161).

The evidence is strongest in support of clozapine mono-

therapy as an intervention for neuroleptic-resistant patients; serum levels of 350 ng/mL or greater have been associated with maximal likelihood of response (162). Given the risk of agranulocytosis, the burden of side effects, and the requirement of white blood cell monitoring, the second-generation agents (risperidone, olanzapine, and quetiapine) are commonly tried before proceeding to clozapine. The appropriate first choice among these agents is unclear; two controlled studies that compared olanzapine and risperidone have produced divergent results, probably reflecting differences in dosing of the two agents and the use of intent-to-treat versus completer analyses (63,163). The focus of this research has been on comparisons of mean responses between groups; predictors of response have not been identified, nor have subgroups of patients that may exhibit preferential response to one agent of the class. Many clinicians express the impression that certain patients do respond preferentially to a single agent of this class. Sequential controlled trials of the newer agents in treatment-resistant patients will be necessary to fully examine this issue.

**Combinations of Antipsychotics**

The practice of combination therapy is gaining widespread popularity in the absence of controlled data in its support (164). In part based on empirical experience and the demonstration that clozapine at optimal doses achieves relatively low degrees of D2 occupancy, European clinicians commonly add low-doses of neuroleptics to clozapine in partially responsive patients (165). Uncontrolled trials and case reports have described benefits associated with the addition of risperidone (4 mg per day) (159,166) and pimozide (167) to clozapine in partially responsive patients. In a small, placebo-controlled trial, addition of sulpiride 600 mg per day to clozapine significantly improved positive and negative symptoms at the end of 10 weeks in 28 subjects (168). Other combinations, most notably olanzapine plus risperidone, are also increasingly employed, often because clinicians perceive improved response during the cross-tapering phase of switching from one to the other. A theoretical rationale for this combination is less apparent, given that each agent produces maximal D2 and 5-HT2 occupancy when appropriately dosed (57). If combined treatment with olanzapine and risperidone is found in suitably controlled study designs to offer advantages over optimal monotherapy with either agent, such a finding would argue in favor of the existence of additional contributory receptor actions unique to each drug.

**Adjunctive Treatments**

A diverse range of adjunctive treatments has been proposed for antipsychotic-resistant schizophrenia, although therapeutic effects generally have been small or inconsistent in controlled trials. Very little data are available from controlled trials augmenting clozapine in partial responders (169). Lithium augmentation frequently has been cited as
the best-established intervention based on positive results from three small studies (170–172); however, two recent placebo-controlled studies found no benefit when well-characterized neuroleptic-resistant patients were treated with lithium (approximately 1.0 mEq/L) added to haloperidol or fluphenazine decanoate (173,174). Augmentation with lithium may enhance response of some patients, particularly in the presence of affective symptoms or excitement (175, 176). Carbamazepine augmentation of conventional neuroleptics has been associated with modest reductions in persistent symptoms, including tension and paranoia, in several controlled trials (177–179), particularly in patients with abnormal EEGs or violence. However, induction of hepatic microsomal enzymes by carbamazepine can substantially lower blood levels of certain antipsychotic agents (180) and in one report, resulted in clinical deterioration (181). Valproate does not significantly affect serum concentrations of most antipsychotic drugs, but results from two small controlled augmentation trials have been inconsistent. Was- 
self and colleagues (182) reported efficacy for negative symptoms and global psychopathology associated with addition of divalproex to haloperidol in a placebo-controlled 12-week trial in 12 schizophrenia patients hospitalized for acute exacerbation. In contrast, Ko and colleagues (183) found no effect when valproic acid was added to conventional neuroleptics in six treatment-resistant patients in a placebo-controlled crossover design. Augmentation with benzodiazepines also has been advocated, in part, because of the potential role of GABAergic agents in modulating dopamine transmission, although the evidence for efficacy is not compelling (184). Short-term, acute treatment with high-dose benzodiazepines may reduce agitation and psychotic symptoms in as many as 50% of patients (185,186), but early reports of benefit of longer-term treatment with benzodiazepines have not been replicated consistently by controlled trials (186,187).

Electroconvulsant Therapy and Transcranial Magnetic Stimulation

The most consistent evidence for efficacy in neuroleptic-resistant patients can be found in the literature describing electroconvulsant therapy (ECT) (188). Response rates between 50% and 80% were observed when ECT or the convulsant, Metrazole, were administered unblinded in neuroleptic-naive patients prior to the introduction of antipsychotic medication (189–191). Three double-blind randomized trials comparing neuroleptic plus ECT versus neuroleptic plus sham-ECT have demonstrated a significantly greater and more rapid reduction in psychotic symptoms (delusions) with the combination treatment during 2- to 4-week trials (192–194). Benefits of ECT were lost, however, at follow-up 10 to 28 weeks after treatment. Predictors of a positive response to ECT include acute onset and brief duration of illness (188,195–198). Mood symptoms in schizophrenia patients have tended to be relatively unresponsive to ECT and a diagnosis of schizoaffective disorder did not predict a favorable response (192–195). Cases describing the successful combination of ECT with clozapine in refractory patients have also been reported, suggesting that augmentation of atypical agents with ECT warrants further investigation (199,200). Recently, interest has focused on the potential use of transcranial magnetic stimulation (TMS) as an alternative to ECT in schizophrenia. TMS has shown promising efficacy in depression (201–203). In a preliminary, sham-TMS controlled crossover study in 12 medication-resistant schizophrenia patients, the frequency and severity of auditory hallucinations were significantly reduced following 12 to 16 minutes of stimulation (204). Improvement of auditory hallucinations persisted for a mean of 14 days (range 1 to 60 days). This is an intriguing area for future research, both as a tool to explore the neural circuits underlying symptoms of schizophrenia as well as a potential treatment option in medication-resistant cases.

Psychosocial Interventions

A particularly promising psychosocial approach to medication-resistant psychotic symptoms is cognitive-behavioral therapy (CBT) (205). CBT for psychosis generally consists of alliance formation, examination, and challenge of psychotic beliefs, and the teaching of self-monitoring and coping skills. Four randomized trials, all performed in the United Kingdom, demonstrated superior efficacy for CBT compared to active control treatments on measures of global psychopathology and positive symptoms among chronic, medicated patients (206–209). A recent metaanalysis determined that the between-groups effect size was .65, favoring CBT over comparison treatments for the response of psychotic symptoms; delusions were generally more responsive than hallucinations (210). Improvements in ratings of psychotic symptoms have been found to persist at follow-up, 1 year after completion of CBT (209). Although therapeutic effects have been impressive, only about half of subjects have displayed improvement in controlled trials (205). Preliminary evidence suggests that patients who exhibit a capacity to entertain alternative explanations for psychotic beliefs at baseline are more likely to respond to CBT (205).

Negative Symptoms

Antipsychotic Monotherapy

Although atypical antipsychotics have generally demonstrated superior efficacy for negative symptoms compared to high-potency conventional agents, the degree of improvement is usually quite modest, leaving substantial levels of residual negative symptoms. For example, across several studies, the effect size of risperidone 6 mg per day compared to placebo on negative symptoms was small (.27) (211). Path analysis has suggested that both risperidone and olanzapine exert direct effects on negative symptoms independent of differences in psychotic, depressive, or extrapyrami-
Adjunctive Agents

Following clozapine’s example as an antagonist of D₂ and 5-HT₂ receptors, investigators combined haloperidol with ritanserin, a relatively selective 5-HT₂₅A and 5-HT₁C antagonist (216). In a 6-week, placebo-controlled trial, addition of ritanserin to haloperidol produced significant reductions in negative symptoms (primarily affective expression and social withdrawal) and depressed mood. Addition of 5-HT₂ blockade may improve negative symptoms by enhancing mesocortical dopamine release. Svensson and colleagues demonstrated that 5-HT₂ blockade increases firing of midbrain dopamine neurons and reverses the effects of N-methyl-D-aspartate (NMDA) antagonism (217) and hypofrontality (218) on A10 dopaminergic neuronal firing. Because the available atypical agents achieve maximal occupation of 5-HT₂ receptors at usual therapeutic doses (57), it is unlikely that augmentation with 5-HT₂ antagonists (e.g., nefazodone) will further improve response of negative symptoms.

Another serotonergic augmentation strategy has involved addition of selective serotonin reuptake inhibitors (SSRIs) to conventional neuroleptics, based largely on early empirical observation (219). Fluoxetine and fluvoxamine significantly improved negative symptoms when added to conventional neuroleptics in three of four controlled trials, producing generally modest effects (220). In one study, fluoxetine 20 mg per day added to depot neuroleptics decreased ratings of negative symptoms by 23% compared to a 12% reduction with placebo; this improvement occurred despite a mean 20% elevation in haloperidol serum concentrations and a 65% increase in fluphenazine levels (221). However, addition of sertraline 50 mg per day to haloperidol produced no symptomatic change in an 8-week, placebo-controlled trial in 36 chronic inpatients with schizophrenia (222). In the only reported controlled trial of SSRI augmentation of an atypical agent, fluoxetine at a mean dose of 49 mg per day produced no improvement in negative symptoms when added to clozapine in 33 patients (223).

Anticholinergic agents are commonly added to conventional antipsychotics for control of EPS (224). The atypical agents vary substantially in their muscarinic anticholinergic activity; clozapine is strongly anticholinergic, whereas quetiapine and risperidone exhibit very low affinity for muscarinic receptors (Table 56.1). Addition of anticholinergic agents to conventional agents was associated with reductions in negative symptoms in one study (225) but not others (176,226–228). Whether primary negative symptoms are improved by anticholinergics, as suggested by Tandon and colleagues (229), cannot be answered by studies in which subjects are treated with conventional agents; by attenuating psychomotor side effects of the neuroleptic, the anticholinergic may be improving secondary negative symptoms only. To address this issue, two small placebo-controlled trials have administered anticholinergic agents to medication-free patients. Negative symptoms were improved by biperiden in one study (230) and were unchanged with trihexyphenidyl in the other (231). Although the efficacy of augmentation with muscarinic anticholinergic agents for negative symptoms remains poorly established, the potential cognitive impairment that these agents can produce is well described (232,233).

Dopamine agonists have also been studied as augmenting agents for negative symptoms. Three of four placebo-controlled trials demonstrated improvement of negative symptoms following a single dose of amphetamine given orally or intravenously (234–237); in one study efficacy for negative symptoms was not affected by coadministration with pimozide (236). However, Casey and colleagues (238) found no clinical benefit in an extended, 20-week placebo-controlled trial of amphetamine augmentation of chlorpromazine. Augmentation trials of psychostimulants added to atypical agents have not been reported.

As discussed elsewhere in this chapter, augmentation strategies for negative symptoms have recently targeted glutamatergic receptors, in part based on the NMDA antagonist model for schizophrenia and the observation that clozapine differs from conventional agents in its effects on NMDA receptor activity (239). Significant improvements in negative symptoms consistently have been produced in placebo-controlled trials by the addition to conventional antipsychotics of agonists at the glycine site of the NMDA receptor. D-cycloserine, a partial agonist at the glycine site, produced a selective, 23% mean improvement of negative symptoms at 6 weeks that, compared to placebo (7% reduction), represented a large effect size (80) (240). The full agonist, glycine, at a dose of 60 g per day produced a 30% mean reduction in negative symptoms and also improved a qualitative measure of cognitive functioning (241). Augmentation with another endogenous full agonist, D-serine 30 mg per kg per day, was associated with significant im-
provements in negative, positive, and cognitive symptoms when added to conventional agents and to risperidone in an 8-week trial (242). Consistent with evidence that clozapine differs from conventional agents in its effects on NMDA receptor responsiveness, glycine, D-cycloserine, and D-serine did not improve negative symptoms when added to clozapine (242–245). Whether strategies that enhance NMDA receptor activation will improve response to other atypical agents remains uncertain, although both olanzapine and quetiapine resemble clozapine in certain models of NMDA receptor responsivity.

**Psychosocial Treatments**
Existing psychosocial approaches have not achieved notable success in the treatment of negative symptoms. Negative symptoms are substantially less responsive to CBT than are psychotic symptoms and patients with prominent negative symptoms are generally poor candidates for CBT (205). Similarly, in a pilot study, Kopelowicz and colleagues (246) found that patients meeting criteria for the deficit syndrome were relatively less likely to benefit from a program of psychoeducation and social skills training than patients without prominent negative symptoms. The presence of negative symptoms also predicts poor outcome in vocational rehabilitation programs for patients with schizophrenia (247). Although most forms of outreach and involvement of deficit syndrome patients in psychosocial programs may improve their quality of life by reducing social isolation and countering apathy, negative symptoms constitute a serious obstacle to participation in such programs and are unlikely to improve with psychosocial treatment.

**Mood Symptoms**

**Antipsychotic Monotherapy**
Depressive symptoms are common during all stages of schizophrenia and are associated with poor outcome, including relapse and suicide (248–250). It is not uncommon for patients to present initially with depression during the prodromal stage, prior to the appearance of psychotic symptoms (251). Approximately 25% of first-episode patients exhibit depression, although estimates of the incidence of comorbid depression vary widely according to choice of diagnostic criteria (251–253). The prevalence of depression as defined by moderate scores on depression rating scales ranges between 25% and 50% in chronic patients (252, 254). Although considerable overlap exists between symptoms of depression and certain negative symptoms (e.g., anhedonia, poor concentration, psychomotor retardation), dysphoria appears to discriminate between the two (255, 256).

Conventional antipsychotics tend to have little effect on comorbid depression, although anxiety and depression associated with acute psychotic exacerbation frequently respond to neuroleptic monotherapy (257,258). However, dysphoric reactions to high-potency conventional agents, although generally not meeting criteria for major depression, can closely resemble the depressive symptoms often associated with the illness (254,259,260). Clozapine, olanzapine, and risperidone have all demonstrated significantly greater efficacy for depressive symptoms compared to conventional neuroleptics in large, double-blind trials (64,211,261). Path analysis suggested that 57% of the superior response of depressive symptoms to olanzapine compared to haloperidol was a direct effect, whereas effects on negative symptoms accounted for only 21% and reductions in EPS accounted for 13% of the difference in depressive symptom response (64). Antidepressant activity of the atypical agents may have important clinical consequences because perceived improvement in anxiety and depression is a strong predictor of compliance and emergence of depressive symptoms often accompanies relapse.

**Adjunctive Agents**
In a placebo-controlled trial reported in 1989, Kramer (258) found that addition of desipramine or amitriptyline 5 weeks after initiating haloperidol to acutely decompensated patients with schizophrenia and depression was associated with poorer antipsychotic response and did not improve depressive symptoms. Subsequently, Siris and colleagues (262, 263) demonstrated that imipramine added to conventional agents in stable outpatients significantly improved depression without adversely affecting psychotic symptoms. In a carefully controlled trial, imipramine 200 mg per day was associated with substantial improvement in depressive symptoms in 42% of patients compared to 12% with placebo. Hogarty and colleagues (176) found that desipramine improved symptoms of depression, anxiety, and psychosis when added to fluphenazine decanoate in a placebo-controlled trial. Benefits of desipramine were only significant in female patients and did not achieve significance until week 12. The investigators noted that improvement of psychotic symptoms might have resulted from successful prophylaxis against depressive episodes, which were associated with worsening of psychosis. Several trials of tricyclic antidepressants added to conventional agents have been reported; this literature generally supports their use for acute and maintenance treatment of depressive symptoms in stable patients (264,265). Augmentation with selective serotonin reuptake inhibitors has been studied primarily as a treatment for negative symptoms—use of these agents in schizophrenia patients with depression is not well studied. Similarly, addition of antidepressants to atypical agents has not been reported in schizophrenia patients with comorbid depression.

**Cognitive Symptoms**

**Antipsychotic Monotherapy**
A wide range of cognitive deficits are usually present at the time of the first psychotic episode (266) and remain stable...
or only slowly progressive during the course of the illness, independent of psychotic symptoms (267–269). Cognitive deficits are particularly prominent in patients meeting criteria for the deficit syndrome (270) and in patients with tardive dyskinesia (271). The latter association may indicate that cognitive deficits are a risk factor for tardive dyskinesia, or alternatively, that the neurotoxic mechanism responsible for irreversible motoric deficits also compromises cognitive functioning. Targeting cognitive impairments is now a major focus of drug development because cognitive deficits are powerful determinants of vocational and social functioning and may influence quality of life (36) more than psychotic symptoms.

The conventional neuroleptics produce small and inconsistent effects on cognitive functioning; sustained attention improved in some studies, whereas motor control (finger tapping) worsened and memory and executive functioning were minimally affected (272). Recent evidence in monkeys indicates that chronic neuroleptic exposure results in decreased prefrontal cortical D1 receptor density after 6 months (273); treatment with a D1 agonist reversed neuroleptic-associated deficits in working memory (274). In normal subjects, clozapine administered as a single 50-mg dose worsened attention, concentration, and motor functioning (275), presumably reflecting sedative and anticholinergic properties. Studies in patients with schizophrenia have found either no effect following a switch to clozapine (276), or improvements in a wide range of cognitive functions, including verbal fluency, attention, and reaction time (37, 277). In general, clozapine, olanzapine, and risperidone have demonstrated superior efficacy compared to conventional agents on tests of verbal fluency, digit-symbol substitution, fine motor function, and executive function (37, 277). Atypical agents least affected measures of learning and memory (37). Enhanced performance with atypical agents could result, in part, from reduced parkinsonian side effects because these tests all measure performance during a timed trial (37). Methodologic issues limit comparisons between atypical agents, however, preliminary evidence suggests that risperidone may be more effective for visual and working memory than clozapine (277). In a 12-month, double-blind trial involving 55 schizophrenia patients randomly assigned to olanzapine (mean dose 11 mg per day), risperidone (mean dose 6 mg per day), or haloperidol (mean dose 10 mg per day), risperidone and olanzapine produced significantly greater improvement in verbal fluency compared to haloperidol, and olanzapine was superior to both haloperidol and risperidone in effects on motor skills, nonverbal fluency, and immediate recall (278). However, this finding is complicated by the high incidence of anticholinergic administration prior to the final cognitive assessment; anticholinergics were prescribed to 73% in the haloperidol group, 45% in the risperidone group, and 15% in the olanzapine group. As in efficacy studies for negative symptoms, dose equivalency is an important factor in trials comparing cognitive effects of atypical agents, particularly because excessive dosing can impair performance on time-sensitive tasks and increase anticholinergic exposure.

**Adjunctive Agents**

Augmentation with glutamatergic agents has shown promise for cognitive deficits in schizophrenia (279). As noted, glycine and D-serine improved ratings of cognitive functioning when added to conventional neuroleptics (241, 280). Both agents improved the “cognitive subscale” of the PANSS compared to placebo, and D-serine was also associated with improved performance on the Wisconsin Card Sort. These findings are of interest given that NMDA antagonists produce in normal subjects deficits in attention and memory similar to those found in schizophrenia (281,282). The partial agonist, D-cycloserine, did not improve cognitive functioning when added to conventional agents in a study that utilized formal cognitive testing, however (240). Positive modulators of the glutamatergic AMPA receptor are also under investigation, as these agents improve performance in tests of learning and memory in animal studies (283). In a preliminary 4-week, placebo-controlled trial involving 19 schizophrenia patients, CX-516, a positive modulator of the glutamatergic AMPA receptor, improved performance on tests of memory and attention when added to clozapine (284). Effect sizes favoring CX-516 over placebo were moderate to large (.5 to 1.2) on tests of cognitive performance.

**Psychosocial Treatments**

Although cognitive remediation treatments have long been used for brain-injured individuals, similar treatment approaches targeting cognitive deficits in schizophrenia are relatively recent. In small studies in which schizophrenia patients practiced graduated cognitive exercises, performance on laboratory measures of attention and memory function improved, although the functional benefits of these gains are not clear (285,286). Brenner and colleagues (287) developed integrated psychological therapy (IPT), a cognitive remediation program in which cognitive exercises are provided in a group format stressing the integration of cognitive skills with social functioning. In a 6-month randomized trial in which patients received IPT or supportive treatment in addition to comprehensive psychiatric rehabilitation, the IPT group displayed greater improvement on the primary outcome measure of interpersonal problem solving and on a laboratory measure of attentional processing (288). This study was conducted prior to the introduction of atypical antipsychotics. Following another approach, Hogarty and Flesher (289) recently developed cognitive enhancement therapy (CET), which combines interactive software and social group exercises to improve socially and behaviorally relevant cognitive functioning. This approach is based on a neurodevelopmental model for cognitive deficits in schizophrenia (290). Preliminary results
from a controlled 1-year trial of CET have also been encouraging (289).

EXPERIMENTAL TREATMENTS AND STRATEGIES

Selective Dopamine Antagonists

There are several lines of evidence suggesting that selective dopamine D4 receptor antagonists may be potential novel antipsychotic drugs. Clozapine has a relatively higher affinity for the D4 versus D2 or D3 receptors (291) (Table 56.1). Not only clozapine, but also a number of clinically efficacious antipsychotics have relatively high affinity for this receptor site (Table 56.1). In addition, an increase in D4 receptors has been reported in the brains of patients with schizophrenia (292). Furthermore, the D4 receptor, enriched in the prefrontal cortex and hippocampus, is located in dopamine terminal fields potentially associated with emotion and cognition, but not with movement, underscoring the potential of this receptor as a target. The selective D4 antagonist, sonepiprazole (U-101387) increases dopamine release in the frontal cortex, but decreases dopamine release in the nucleus accumbens in rats (293). Sonepiprazole attenuates apomorphine-induced impairment of prepulse inhibition in rats (294). It also antagonized the decrease in c-fos expression in the medial prefrontal cortex and neurotensin mRNA in the nucleus accumbens produced by repetitive amphetamine administration in rats, suggesting possible antipsychotic action of the agent (295). Sonepiprazole is currently in Phase II clinical trials in patients with schizophrenia (293). An initial clinical trial with another highly selective D4 antagonist, L-745,870, failed to demonstrate any antipsychotic activity in the treatment of schizophrenia (296, 297). Although the single dose tested makes it difficult to draw firm conclusions regarding the potential efficacy of D4 antagonists as antipsychotic agents (298), this drug actually caused a worsening of symptoms (297). Similarly, NGD-94-1 also did not show clinical efficacy in limited trials in schizophrenics (293). More extensive testing of D4 antagonists in patients with schizophrenia will be necessary to adequately assess the therapeutic potential of such drugs.

Dopamine Partial Agonists

Partial dopamine agonists are agents with good affinity for one or more dopamine receptors, but with intrinsic activity less than dopamine (3). Thus, such drugs may antagonize the actions of dopamine, yet by agonistic actions, activate other dopamine-related functions (299). It has been proposed that some D2-like dopamine agonists have a greater affinity for autoreceptors than for heteroreceptors. The action of these agonists at autoreceptors would induce a receptor-mediated inhibition of both the synthesis and release of dopamine from nerve terminals, without producing significa-
in perception, mood regulation, and motor control (313). Available evidence indicates that 5-HT₁₉ receptor stimulation plays a role in promoting the synthesis and release of dopamine, either by effects on firing rates of dopamine neurons, or via heteroreceptors on dopamine nerve terminals, or both (312–315). 5-HT₂₄ receptor blockade may therefore contribute to “normalizing” levels of dopamine release (316) and theoretically possess antipsychotic activity.

M-100907 (formerly MDL-100,907) is a selective 5-HT₂₄ receptor antagonist devoid of affinity to dopamine receptors (21). Like the atypical antipsychotics, it decreases the firing rate of A10, but not A9, neurons after chronic treatment (317). M-100907 inhibited the behavioral response not only to amphetamine and cocaine (316–318), but also to NMDA receptor antagonists at doses that did not affect spontaneous activity given alone in rodents (319–321). M-100907, like clozapine, markedly increases dopamine release in the medial prefrontal cortex in rats (322), suggesting that the agent may have efficacy for negative symptoms. In contrast, it attenuates dopamine release in the nucleus accumbens induced by the NMDA receptor antagonist MK-801 (323). M-100907 also antagonized MK-801-induced prepulse inhibition deficit in rats (324). Further, in electrophysiologic studies, it prevented phencyclidine (PCP)-induced blockade of NMDA responses (325). These preclinical results suggest that M-100907 can attenuate variable responses to NMDA receptor antagonists in vivo and modulate NMDA receptor-mediated neurotransmission. M-100907, however, exhibited lower antipsychotic efficacy compared with haloperidol in Phase III clinical trials (326). Insufficient data are currently published to adequately judge the efficacy of the drug.

It has been suggested that the partial agonist activity of clozapine at 5-HT₁₉ receptors may contribute to its therapeutic action (313,327). Preclinical studies have suggested that serotonin 5-HT₁₉ agonists may potentiate the antipsychotic activity of dopaminergic antagonists (328). Activation of inhibitory 5-HT₁₉ autoreceptors may also counteract the induction of EPS owing to striatal D₂ receptor blockade (329). Further, in schizophrenic patients, increased 5-HT₁₉ receptor binding was seen in the prefrontal cortex (330,331). Based on these preclinical data, compounds that act as serotonin 5-HT₁₉ agonists are being developed as potential antipsychotic compounds.

S-16924 is a novel, potential antipsychotic agent with high affinity for dopamine D₂/₃, α₁-adrenergic, and serotonin 5-HT₂₄ receptors, similar to that of clozapine, in addition to being a potent partial 5-HT₁₉ agonist (332). Reflecting its partial agonist actions at 5-HT₁₉ receptors, it attenuates cerebral serotonergic transmission, and preferentially facilitates dopaminergic transmission in mesocortical as compared to mesolimbic and nigrostriatal pathways (333,334). S-16924 exhibited a profile of potential antipsychotic activity and low EPS liability in animal behavioral models, similar to clozapine (332).

Muscarinic Agents

In patients with Alzheimer’s disease (AD), cholinesterase inhibitors (e.g., physostigmine) have been shown to not only improve cognition, but also reduce hallucinations, delusions, suspiciousness, and other behavioral disturbances sometime associated with the illness (335–338). Similar positive effects on cognitive and psychotic-like symptoms in AD have been observed after treatment with the direct muscarinic agonist, xanomeline (339). In addition, high doses of some muscarinic agonists produce psychotic-like symptoms and memory loss (340). Thus, it has been proposed that muscarinic agonists could be novel potential treatments for positive and cognitive symptoms of schizophrenia (341).

Recent findings that partial agonists of m₂/m₄ muscarinic receptors are active in animal models that predict antipsychotic activity suggest potential usefulness of muscarinic agonists in the treatment of schizophrenia (342). The drug (5R,6R) 6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (PTAC) is a muscarinic partial agonist at muscarinic m₂ and m₄ receptor subtypes (342). PTAC acts as a functional dopamine antagonist in many paradigms (consistent with known dopamine-acetylcholine interactions), although it has minimal or no affinity for central dopamine receptors. PTAC attenuates apomorphine-induced climbing (341), inhibits the effects of D₁ and D₂ dopamine receptors agonists in 6-hydroxydopamine-lesioned rats, and antagonizes amphetamine-induced Fos induction and hyperactivity (343). In addition, after chronic administration, PTAC reduced the number of spontaneously active dopamine cells in the ventral tegmental area, but not the substantia nigra (343). Such selective effects on the mesocorticolimbic dopamine projection neurons are similar to those observed for clozapine and olanzapine (344,345). The notable preclinical data of the effects of PTAC provide strong encouragement to examine the potential therapeutic effects of M₂/M₄ muscarinic agonists in schizophrenic patients. Among the agents that have been developed for the treatment of AD that are being examined in schizophrenia are donepezil, metrifonate, galantamine, and xanomeline.

Glutamatergic Agents

The NMDA Receptor Hypofunction Hypothesis of Schizophrenia

Since the late 1950s, the anesthetics phencyclidine (PCP) and ketamine have been known to induce “emergence reactions” in 40% to 50% of individuals during the recovery from anesthesia, that resembles some features of schizophrenia (346). Recent work has confirmed and extended the early clinical studies and has demonstrated that subanesthetic doses of ketamine can induce positive, negative, and cognitive schizophrenia-like symptoms in normal humans.
(281,347). In chronic stabilized schizophrenic patients, subanesthetic doses of ketamine can also exacerbate cognitive impairment and in some cases produce specific hallucinations and delusional ideation remarkably similar to those experienced during active phases of the patients’ illness (282,348,349). Both ketamine and PCP are potent non-competitive NMDA receptor antagonists. These drugs bind to a site within the calcium channel of the NMDA receptor complex, and thereby interfere with calcium flux through the channel. Competitive NMDA receptor antagonists (i.e., drugs that inhibit binding to the glutamate recognition site) are also psychotomimetic (350). The ability of NMDA antagonists to induce a spectrum of schizophrenia-like symptoms has led to the hypothesis that hypofunction of NMDA receptors is involved in the pathophysiology of schizophrenia (346,351–353).

**Antipsychotic Drug Actions in Relation to the NMDA Receptor Hypofunction**

The well-documented psychotomimetic effects of NMDA antagonist in human suggest that effects of the drugs in experimental animals could present useful pharmacologic models of schizophrenia. In our recent studies, striking effects of subanesthetic doses of ketamine were observed on regional brain patterns of $^{14}$C-2-deoxyglucose (2-DG) uptake in both rats (354,355) and mice (356). Ketamine induces robust and neuroanatomically selective patterns of brain metabolic activation, with especially large effects observed in the hippocampus, nucleus accumbens, and medial prefrontal cortex (354,355). Pretreatment of rats with clozapine or olanzapine can completely block these effects of ketamine (357,358). However, the typical antipsychotic haloperidol failed to antagonize the brain metabolic activation induced by ketamine (357). Similarly, clozapine and olanzapine, but not haloperidol, effectively block NMDA antagonist-induced electrophysiologic responses (325), deficits in prepulse inhibition (359,360), and deficits in social interactions (361). Thus, in a wide range of experimental paradigms, atypical antipsychotic drugs selectively antagonize the consequences of experimentally induced NMDA receptor hypofunction, raising the possibility that the therapeutic effects of these agents may be associated with a similar neurochemical action (362).

**Therapeutic Potential of Glycine Site Agonists**

If reduced NMDA receptor function is involved in the pathophysiology of schizophrenia, then drugs that enhance NMDA receptor function could be therapeutic agents and potentially improve upon, or supplement, current antipsychotic treatments (13). Direct agonists of the NMDA receptor may not be feasible candidates in this regard, because of the propensity of such drugs to produce excessive excitation and seizures.

Glycine is a positive allosteric modulator and obligatory coagonist at the NMDA receptor (363) and this allosteric regulatory site represents a potential target for drugs to augment NMDA-mediated neurotransmission. Preclinical studies have demonstrated that glycine-site agonists reverse the effects of noncompetitive NMDA receptor antagonists (364). There have been several clinical studies to test effects of different glycine site agonists in patients with schizophrenia. The earliest studies in this regard used glycine in doses of 5 to 15 g per day and obtained inconsistent results (365, 366). In more recent work with glycine, higher doses were administered (30 to 60 g per day) and more robust and consistent effects were found, primarily in the improvement of negative symptoms (241,367,368).

D-cycloserine is a partial agonist at the glycine regulatory site on the NMDA receptor. Thus, at low dose of the amino acid, stimulatory responses are observed, but at higher doses, D-cycloserine blocks the effects of endogenous glycine. D-cycloserine has been tested in patients with schizophrenia, and in a very narrow dose range, the agent was shown to improve negative symptoms when administered alone (369), and when added to conventional antipsychotic treatment regimes (240, 370). The “inverted U”-shaped dose response may result from the partial agonist properties of D-cycloserine, because antagonism of the actions of endogenous glycine would be predicted at higher doses of the drug. Interestingly, when D-cycloserine was administered in conjunction with clozapine, the negative symptoms of the patients worsened (244,371). A ready explanation for these effects is not available, but understanding the mechanisms involved in the worsening of negative symptoms after administration of D-cycloserine to clozapine-treated patients may be an important clue in understanding the actions of both of these drugs. The poor penetration of the blood–brain barrier by glycine, and the partial agonistic properties of D-cycloserine, appear to make these agents less than optimal for providing pharmacologic agonism of the glycine regulatory site on the NMDA receptor (13).

D-serine is a full agonist on the strychnine-insensitive glycine site of NMDA receptor (372) and is more permeable than glycine at the blood–brain barrier, thus requiring a lower dosage. In a recent clinical trial, D-serine (30 mg per kg per day) added to neuroleptic treatment in treatment-resistant patients with schizophrenia demonstrated significant improvements not only in negative and cognitive symptoms but also positive symptoms, which is different from glycine (280). These data, together with the results of the clinical investigations with glycine and D-cycloserine (346), offer promise for the therapeutic potential of enhancing NMDA receptor function as a strategy for the pharmacotherapy of schizophrenia. Recently, Wolosker and colleagues (373) purified an enzyme from Type II astrocytes that converts L-serine to D-serine. It may be that effectors of this enzyme (directly or through possible receptor-mediated regulation) can provide a mechanism to modulate NMDA
function. Examining the effects of synthetic compounds with greater potency and full agonistic activity at the glycine regulatory site could be an intriguing line of future research. There are, however, no such compounds available for testing at present.

**Potentiation of NMDA Receptor Function by Inhibition of Glycine Uptake**

Glycine transporters have been identified on both neuronal and glial cells in the central nervous system. A function of these transporters has been suggested to control the extracellular glycine concentration (374). Although there is some controversy as to whether the glycine regulatory site on the NMDA receptor is saturated under physiologic conditions, recent data demonstrate that inhibition of glycine transport by glycine transporter type 1 antagonist can potentiate electrophysiologic effects of NMDA (374,375). Furthermore, the glycine uptake inhibitor glycyldecylylamide attenuated PCP-induced hyperactivity more potently than glycine (364,376). These preclinical data suggest that inhibition of glycine uptake could represent a feasible approach to potentiate NMDA receptor-mediated neurotransmission and, possibly, treat schizophrenic patients.

**Glutamate Release-Inhibiting Drugs**

A number of studies have indicated that administration of relatively low (subanesthetic) doses of NMDA antagonists induces behavioral and brain metabolic activation in experimental animals and humans (362). Consistent with these data, NMDA antagonists increase glutamate release in rats (377). In contrast to the increase in glutamate release by subanesthetic doses of ketamine, anesthetic doses of the drug decreased glutamate levels (377). The effect of different doses of ketamine on glutamate levels is consistent with our observations of increased 2-DG uptake in response to a subanesthetic dose, and reduction in 2-DG uptake in response to an anesthetic dose of ketamine (354).

The stimulatory effect of NMDA receptor antagonism presumably results from disinhibitory actions, perhaps by reducing excitatory input to inhibitory interneurons (362). In hippocampal formation, GABAergic interneurons are more sensitive to the effects of NMDA antagonists than the glutamate-containing pyramidal cells (378), providing support for the hypothesis that NMDA antagonism could result in excitatory effects by disrupting recurrent inhibitory circuits (362).

If behavioral activation induced by NMDA antagonists is related to increased glutamate release, pharmacologic agents that decrease glutamate release should block the effects of the drugs. Glutamate release can be inhibited by Na⁺-channel blockers, Ca²⁺-channel blockers, K⁺-decreasing agents, toxins that prevent fusion of vesicles with the presynaptic membrane, and presynaptic group II metabotropic glutamate autoreceptor agonists (379–381).

Administration of LY-354740, a group II metabotropic glutamate receptor agonist, blocked both behavioral activation and increased glutamate release induced by PCP in rats (382). In humans, Anand and co-workers (381) found that lamotrigine, a new anticonvulsant agent that inhibits glutamate release, can reduce the ketamine-induced neuropsychiatric effects. These data suggest the possibility that glutamate release-inhibiting drugs (e.g., LY-354740 and lamotrigine) could be useful in the treatment of schizophrenia.

**AMPA/Kainate Receptor Antagonists**

The increased release of glutamate observed in response to NMDA antagonist could mediate some of the behavioral actions of the drugs by activation of non-NMDA receptors, including α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors (377). In support of the hypothesis that behavioral effects of NMDA antagonists relate to increased glutamate release, administration of an AMPA/kainate receptor antagonist, LY-293558, partially reversed impairment of working memory induced by subanesthetic doses of ketamine in rats (377). Furthermore, AMPA/kainate receptor antagonists reduce NMDA antagonist-induced hyperlocomotion (383–385) and neurodegeneration (386). These data suggest that AMPA/kainate receptor antagonists may have utility for treatment of cognitive deficits in which NMDA receptor hypofunction is suspect (377).

**Potential of Positive Modulators of AMPA Receptors**

In apparent contrast to the postulated utility of AMPA/kainate receptor antagonists as antipsychotics, ampakines, a class of compounds that allosterically enhance AMPA receptor function, have also been suggested to represent potential adjunctive treatments for schizophrenia. Ampakines enhance excitatory (glutamatergic) transmission, facilitate long-term potentiation, learning, and memory in rodents (387,388), and have synergistic effects with typical and atypical antipsychotics on blocking behavioral effects of methamphetamine (389). In addition, preliminary results suggest that chronic administration of an ampakine (CX-516) can improve negative and cognitive symptoms in schizophrenia patients that also receive clozapine (284). Thus, such findings are paradoxical with regard to the foregoing discussion of the hypothesis that excessive glutamate release may be involved in behavioral effects of reduced NMDA receptor function. Further clinical experience with the effects of positive and negative modulators of non-NMDA glutamate receptors will be needed to clarify the potential of these compounds for treatment of schizophrenia (3).
Protein Kinase C Inhibitors

Accumulating evidence from Manji and colleagues has identified the family of protein kinase C (PKC) isozymes as a common target in the brain for the long-term action of the two structurally highly dissimilar antidepressant agents, lithium and valproate (390). Chronic treatment of rats with lithium or valproate induces a reduction in the levels of two PKC isozymes, α and ε, in the frontal cortex and hippocampus, as well as a reduction in the expression of a major PKC substrate, myristoylated alanine-rich C kinase substrate (MARCKS), which has been implicated in long-term neuromodulatory events in the developing and adult brain (391). In view of the critical role of the PKC signaling pathway in the regulation of neuronal excitability, neurotransmitter release, and long-term synaptic events, Manji and associates postulated that the attenuation of PKC activity might have antidepressant efficacy. In a pilot study, they found marked antidepressant efficacy of a potent PKC inhibitor tamoxifen, which is also a synthetic nonsteroidal antiestrogen, in the treatment of acute mania (392). Their heuristic preliminary data suggest that PKC inhibitors may represent a novel class of antidepressant agents for the treatment of bipolar disorder, and deserve further study in psychiatric syndromes.

Steroidal Agents

Estrogen

The gender effect of delayed onset (by approximately 2 to 5 years) and relatively reduced symptom severity in females has been consistently observed in schizophrenia (393–395). Some, but not all, researchers have found an additional smaller peak of onset of schizophrenia for women at age 40 to 45 years, which is a time of decreasing levels of estrogen associated with menopause (395,396). The inverse relationship between estradiol levels and specific psychopathology, especially positive symptoms, was also observed over the menstrual cycle in premenopausal women with schizophrenia (397,398). The indirect clinical evidence suggests a potential role for estrogen in delaying the onset or attenuating the severity of psychotic symptoms associated with schizophrenia (393,395). In animal behavioral studies, estrogen reduces amphetamine- and apomorphine-induced stereotypy, as well as enhances neuroleptic-induced catalepsy (399). In addition, preclinical biochemical studies have shown that estrogen can alter dopamine D2 receptor density and affinity in the brain (399), whereas the effect is dependent on the time course of the administration (395). These findings suggest a neuroleptic-like effect of estrogen, and may have important implications for the prevention and therapy of schizophrenia. To date, there have been few treatment studies examining the effect of estrogen in patients with schizophrenia. Lindamer and associates (395) presented a case report of a postmenopausal woman with schizophrenia who had an improvement in positive symptoms with estrogen augmentation of neuroleptic medication. Long-term larger double-blind trials are crucially needed to evaluate the efficacy of estrogen in conjunction with neuroleptic treatment on psychotic symptoms in women with schizophrenia.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S) are neuroactive neurosteroids that represent steroid hormones synthesized de novo in the brain and acting locally on nerve cells (400). Although DHEA and DHEA-S are the most abundant circulating steroid hormones in humans, their precise physiologic roles remain to be elucidated. In humans, DHEA levels in blood rise dramatically at puberty and sustain a monotonic decline with age, reaching very low levels in late life. In vitro data suggest that DHEA and DHEA-S enhance neuronal and glial survival and differentiation in mouse embryonic brain tissue cultures (401–403). In addition, DHEA-S shows marked neuroprotective ability against the glutamate-induced toxicity (404) and oxidative stress (405). In rodents, DHEA has been demonstrated to be a positive modulator of the NMDA receptor. In both the adult rat brain and developing mouse brain, DHEA-S was shown to potentiate substantially physiologic responses to NMDA (403,406,407). The enhancement of physiologic response to NMDA by DHEA has been suggested to result from agonistic actions at s1 receptors in the brain (407). Consistent with a positive modulatory action of DHEA at the NMDA receptor, the neurosteroid has been demonstrated to enhance memory in mice (408–411). Moreover, DHEA-S attenuates NMDA receptor antagonist MK-801-induced learning impairment via an interaction with s1-receptors in mice (412). These preclinical studies provide the neurobiological rationale for the clinical studies to explore the potential utility of DHEA to treat the NMDA receptor hypofunction postulated to occur in schizophrenia. In chronic schizophrenics, significantly lower morning levels of plasma DHEA were observed (413). Further, there are a number of earlier case reports suggesting that DHEA may be useful in the treatment of schizophrenia, especially for negative symptoms (414–416), although these trials were not well controlled. A recent double-blind study of patients with major depression suggests that DHEA has antidepressant effects (417). Although the mechanism of action of DHEA and DHEA-S has to be further characterized, the possibility that these compounds may have efficiency in schizophrenia should be explored.

Phospholipid Compounds

Membrane Phospholipid Hypothesis of Schizophrenia

The membrane phospholipid hypothesis of schizophrenia originated with suggestion by Horrobin (418) that schizo-
Phenomena might be caused by a prostaglandin (PG) deficiency. The proposal was based on several clinical observations of a relationship between pyrexia and the transient dramatic remission of psychosis, the relative resistance to PG-mediated pain and inflammation and reduced rate of rheumatoid arthritis in patients with schizophrenia, and the observation that PGE$_1$ injected into the CSF of mammals could produce catalepsy (419). Because PGs are derived from membrane essential fatty acid (EFA), Horrobin and colleagues (420) hypothesized that schizophrenia involves a failure to produce PGE$_1$ from EFA precursors. Interestingly, over two decades ago, it was suggested that the structure and pharmacologic actions of clozapine are consistent with its being a PGE analogue (420). PGEs are potent stimulators of cAMP formation, and cAMP inhibits phospholipase A$_2$ (PLA$_2$). In fact, clozapine treatment induced a dramatic rise in erythrocyte membrane concentrations of the major cerebral fatty acids, arachidonic acid (AA) and docosahexaenoic acid (DHA) (421). Thus, a generally unrecognized mechanism of action of clozapine may be on membrane phospholipid composition, in addition to its receptor-blocking profile (421).

The specific EFA content of synaptic membrane plays a significant role in modifying neuronal function. The changes in membrane EFA concentrations alter the biophysical microenvironment and hence, structure and function of membrane proteins, including neurotransmitter receptors, ion channels, and enzymes (419). EFAs also contribute to cellular regulation by acting as a source of precursors for second messengers in intracellular and intercellular signal transduction (419).

In rat models, changes in brain fatty acid concentrations produced by chronic dietary omega-3 fatty acid deficiency alter dopaminergic and serotonergic neurotransmission (422) and induce a decrease in D$_3$ and increase in 5-HT$_2$ receptor density in the frontal cortex (423). Impaired behavioral performance and learning are observed in omega-3 deficient rats (424) and have been hypothesized to reflect changes in attention, motivation and reactivity consistent with a deficit in the function of prefrontal dopamine pathways (419).

The phospholipid hypothesis of schizophrenia has been supported by the accumulating consistent clinical findings in schizophrenic patients that indicate reduced levels of erythrocyte membrane EFA, elevated serum and platelet PLA$_2$ activity (probably owing to accelerated breakdown of membrane phospholipids), and 31-phosphorus cerebral magnetic resonance spectroscopy (MRS) evidence of decreased synthesis and increased breakdown of phospholipids in the prefrontal cortex (419). Furthermore, phospholipid hypotheses are consistent with both dysfunction of multiple neurotransmitter systems and neurodevelopmental abnormalities associated with aberrant cell remodeling, apoptosis, or migration (425).

**Omega-3 Fatty Acid**

The membrane EFA or PG deficiency hypotheses have provided the rationale for attempts to treat symptoms of schizophrenia with supplementation of PG precursors, including omega-6 and omega-3 fatty acids and PGE$_1$. Among the studies of these compounds conducted to date, omega-3 EFA treatment has consistently yielded positive results. Two small open trials and a single double-blind trial suggest supplementation with omega-3 eicosapentaenoic acid (EPA) may improve residual symptoms and tardive dyskinesia when added to standard neuroleptic treatment in schizophrenic patients (419). Surprisingly, the more recent case report by Puri and colleagues (426) demonstrates a dramatic and sustained efficacy of omega-3 EPA on both positive and negative symptoms of schizophrenia in a drug-naive patient without any adverse side effects. In addition, cerebral atrophy, observed before omega-3 EPA treatment, was reversed by 6 months of EPA treatment; however, small trials and a single case report make it difficult to draw firm conclusions regarding the potential efficacy of omega-3 EPA. A recent double-blind placebo controlled study of omega-3 EPA as an adjunctive treatment to antipsychotic drugs found no difference between placebo and omega-3 EPA (427).

**Trophic Factors**

There is converging evidence that an abnormal neurodevelopmental process is accountable for at least a proportion of the pathophysiology of schizophrenia (428). The neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3/4/5 play a decisive role in a neurodevelopmental process, including neuronal and glial differentiation, migration, proliferation, and regeneration (429). They are not only active during embryogenesis and organogenesis, but also influence the synaptic organization and synthesis of neurotransmitters in the adult brain, and are therefore involved in the maintenance of neural plasticity (429). Thus, pathologic alterations of the neurotrophic factor system may lead to neural maldevelopment, migration deficits, and disconnections, which are proposed to be the characteristic pathogenetic features of the maldevelopmental hypothesis of schizophrenia (429). A more recent pathophysiologic theory of schizophrenia suggests that it is involved in a limited neurodegenerative process reflected by the progressive and deteriorating clinical course of the illness (430). If neurotrophic factors salvage degenerating neurons, facilitate desirable synaptic connections, and hence, halt the progression of neurodegenerative process of schizophrenia, drugs that selectively stimulate the production of neurotrophic factors could represent a new approach to forestall the progression of schizophrenia and prevent morbidity from increasing (431). However, the lack of consistent evidence supportive
of pathophysiologic progression in schizophrenia has been a weakness of this hypothesis (430). Recently, Riva and associates (432) found that acute or chronic administration of clozapine increased basic fibroblast growth factor (FGF-2) mRNA and protein in the rat striatum, suggesting neuroprotective activity of clozapine. It has been proposed that small molecules that boost the endogenous levels of BDNF or NT-3 might be useful for treating temporally protracted and severe forms of neurodegenerative disease, such as AD or Parkinson’s disease (433). Although neurotrophic factors are unable to cross the blood–brain barrier, potential alterations to administration of these factors are transplantation of neurotrophic factor-producing cells, direct transfection of neurotrophic factor gene, and development of compounds that modulate endogenous neurotrophic factor homeostasis and/or the influence their signal transduction mechanisms (429). The augmentation therapy with neurotrophic factors suggests novel and innovative pharmacotherapeutic, but as yet unproved strategies for schizophrenia.

CONCLUSION

The therapeutic armamentarium for the treatment of schizophrenia has become rich and varied in the half century since the inception of the pharmacologic era marked by the introduction of chlorpromazine. We now have the capacity to control many of the symptoms of the disorder and restore the lives of patients. Much remains to be done in terms of drug discovery of new and novel agents and the determination of their optimal use in conjunction with psychosocial and adjunctive therapies; however, there is reason to be optimistic that future progress will be relatively swift.

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