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THERAPEUTICS OF SCHIZOPHRENIA

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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 D_2 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

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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 D_2 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 D_2 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 D_2 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 D_2 receptor occupancy of 65% to 70% (15–18), and D_2 occupancy greater than 80% significantly increases the risk of EPS (15). Thus, a threshold between 65% and 80% D_2 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 D_2 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 D_2 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 D_2 receptor density and D_{2L} 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 D_2 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 α_1- and α_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 α_2-antagonist idazoxan to the regime of patients treated with the typical neuroleptic fluphenazine resulted in improved treatment responses in patients refrac-

TABLE 56.1. AFFINITY OF ANTIPSYCHOTIC DRUGS FOR HUMAN NEUROTRANSMITTER RECEPTORS (Ki, nM)[a]

Receptor	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Iloperidone	Haloperidol
D_1	290	580	52	1,300	130	410[c]	320	120
D_2	130	2.2	20	180	3.1	0.52[c]	6.3	1.4
D_3	240	9.6	50	940	7.2	9.1[c]	7.1	2.5
D_4	47	8.5	50	2,200	32	260[c]	25	3.3
5-HT_{1A}	140	210	2,100	230	2.5		93	3,600
5-HT_{1D}[a,b]	1,700	170	530	>5,100	2			>5,000
5-HT_{2A}	8.9	0.29	3.3	220	0.39	20[d]	5.6	120
5-HT_{2C}	17	10	10	1,400	0.72		43	4,700
5-HT_6	11	2,000	10	4,100	76	160[e]	63	6,000
5-HT_7	66	3	250	1,800	9.3	15[e]	110	1,100
α_1	4	1.4	54	15	13	57[d]	1.4[d]	4.7
α_2	33	5.1	170	1,000	310		160	1,200
H_1	1.8	19	2.8	8.7	47		470[d]	440
m_1	1.8	2,800	4.7	100	5,100			1,600

[a] Values are geometric means of at least three determinations.
[b] Bovine.
[c] CHO cells.
[d] Rat.
[e] HEK cells.
From Duncan GE, Zorn S, Lieberman JA. Mechanisms of typical and atypical antipsychotic drug action in relation to dopamine and NMDA receptor hypofunction hypotheses of schizophrenia. *Mol Psychiatry* 1999;4:418–428. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 1999;20:612–627. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996;317:417–423.

tory to treatment with fluphenazine alone (49). However, there has been no subsequent confirmation of the effects of α_2 antagonists as adjuncts to typical neuroleptic treatment, and it has been suggested that α_2 agonists may actually be useful for treating cognitive deficits of the disease (50).

Olanzapine is a closely related in chemical structure to clozapine, and 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 D_2 and 5-HT_{2A} receptors (51,52). Olanzapine is more potent at 5-HT_{2A} than D_2 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-HT_{1A} and 5-HT_7 receptors in comparison to olanzapine (Table 56.1).

Quetiapine is another drug with greater relative affinity for 5-HT_{2A} than for D_2 receptors, but also some affinity for α_1-adrenergic and H_1 receptors (53) (Table 56.1). Interestingly, quetiapine produces only transiently high striatal D_2 occupancy in schizophrenic patients, although the study has clinical and technical limitations (54). Ziprasidone has potent 5-HT_{2A} and D_2 affinities, and like clozapine, it shows 5-HT_{1A} agonist properties that could potentially act as protective effects on the development of EPS. Ziprasidone also has significant affinity for 5-HT_{1D} and 5-HT_{2C}, as well as H_1 and α_1-adrenergic receptors (55) (Table 56.1). Iloperidone has in addition to affinity for 5-HT_{2A} and $_{1A}$ and $D_{2,3}$ receptors, also affinity for the α_1- and α_{2c}-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 D_2 receptors suggest that D_2 receptor antagonism could be a predominant mechanism of action of these atypical drugs (56,57). Clozapine, however, does not exhibit high levels of D_2 receptor occupancy at therapeutically effective dose (15,57,58), suggesting that D_2 receptor antagonism alone cannot explain the greater therapeutic efficacy of clozapine (13). The low occupancy of striatal D_2 receptors by clozapine could account for its low EPS liability (20,58, 59).

Clozapine, risperidone, and olanzapine occupy more than 80% of 5-HT_{2A} receptors in the therapeutic dose rage in humans (15,56–58,60). Although 5-HT_{2A} 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).

To date, clozapine is the only drug that has proven efficacy in treatment-refractory schizophrenia (68,69). The efficacy rates for clozapine in treatment-refractory patients vary from 20% to more than 70% (11,70,71). In some studies, risperidone does not appear to be as effective as clozapine in treatment-resistant schizophrenic patients (72–74); however, Bondolfi and associates (75) found no difference between risperidone and clozapine in treatment-resistant patients. In this latter study, certain methodologic issues may have led to an overestimation of the efficacy of both clozapine and risperidone, and there are questions as to whether the patient population studied represented ''truly resistant'' patients (69). Further investigation is necessary to adequately compare the relative efficacy of risperidone and clozapine in treatment-resistant patients. Olanzapine was found to be more effective than haloperidol (74,76), but not chlorpromazine (77), in treatment-refractory patients. In a recent randomized double-blind study of treatment-resistant schizophrenia, olanzapine and clozapine had similar antipsychotic efficacy (74). Additional studies are needed to reach definitive conclusions regarding efficacy of the newer atypical antipsychotics in treatment-resistant schizophrenia. Results of studies investigating the effects of atypical antipsychotics in treatment-resistant patients are discussed elsewhere in this chapter.

The efficacy of atypical antipsychotics in treating primary negative symptoms has not been clearly demonstrated (61). Thus, the choice of atypical drugs for patients with predominantly negative symptoms is less clear (8). In addition, the effects of atypical antipsychotics on cognitive impairment have not yet been clearly proved. A metaanalysis of 15 studies (only three of which were double-blind) of atypical antipsychotics and cognitive impairment in patients with schizophrenia suggests that they may improve attention and executive function (37). Available results, however, are relatively inconsistent and modest in effect size. Furthermore, there are statistical limitations and a lack of standard conventions in the studies of cognition (78). It appears that there could be significant differences among the atypical drugs in terms of what types of cognition they improve.

Atypical antipsychotics have been associated with a reduction in the incidence of suicidality, which may be relevant to antidepressant effects of these agents, at least in part (6). Clozapine, risperidone, and olanzapine, in particular, appear to have beneficial effects on the depressive component of schizophrenia (6,65) (Table 56.2).

Although atypical drugs have shown some instances of superior efficacy in comparison with conventional drugs, they are not effective in all patients and against all symptom dimensions of psychotic disorders (Table 56.2). It is clear

TABLE 56.2. CLINICAL AND SIDE-EFFECT PROFILE OF ATYPICAL ANTIPSYCHOTIC DRUGS

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
Clinical effect					
Psychotic symptoms	+++	+++?	+++?	++	++
Negative symptoms	+	+	+	+	+
Cognitive symptoms	++?	++?	++?	?	?
Mood symptoms	+++	++	+++?	++?	++?
Refractory symptoms	+++	+++?	+++?	++?	++?
Side effect					
EPS	—	++[a]	+[a]	—	+[a]
TD	—	+	?	?	?
Prolactin elevation	—	+++	—	—	—

[a] 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.
From Dawkins K, Lieberman JA, Lebowitz BD, et al. Antipsychotics: past and future. National Institute of Mental Health, Division of Services and Intervention Research Workshop, July 14, 1998. *Schizophr Bull* 1999;25:395–404.

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 ($\geq$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 olanzapine. 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 conventionals 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 D_2 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

averaged 42%. Similar surveys have not been conducted looking specifically at atypical agents, although it is generally believed that reduced relapse rates reported with olanzapine and clozapine may reflect, in part, improved compliance (97,126). Factors contributing to noncompliance are complex and probably involve the patient's perception of benefits and side effects of medication, as well as the patient's level of insight. Compliance can be compromised by psychosis, agitation, and comorbid substance abuse (137, 138). Van Putten (139) studied compliance in 85 schizophrenia patients chronically treated with conventional neuroleptics and determined that 46% took less antipsychotic medication than prescribed. Medication refusal was associated with an early dysphoric response, which Van Putten attributed to subtle akathisia. Analysis of responses by 150 schizophrenia patients to a "Drug Attitude Inventory" revealed that, based on responses to 10 items, 89% of patients could be correctly assigned to compliant versus noncompliant categories as determined by clinician assessment of compliance (140). The strongest predictor of compliance was a positive experience with medication—this factor accounted for 60% of the total variance, whereas the factor representing a negative subjective experience accounted for 12%. Factors representing attitudes and beliefs about medication had minimal predictive power. Other studies have also found that a patient's perception of benefit from medication is the strongest predictor of compliance (141). Whereas many clinicians expect atypical agents to achieve higher levels of compliance by virtue of reduced or absent EPS, this view may seriously underestimate the impact of other side effects. Two studies have found that clinicians tend to misjudge the relative distress produced by different medication side effects (142,143). Side effects associated with certain atypical agents, such as sedation, patients rated weight gain, drooling, and sexual dysfunction as more distressing than EPS in these surveys (142–144). The advantage of atypical agents in terms of compliance may stem less from their reduced EPS and more from their improved efficacy for symptoms of anxiety, depression, and tension. Whether targeting cognitive deficits and impairment in insight will improve compliance remains to be seen.

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 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 observer-rated 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 D_2 receptor occupancy in excess of 65% (18,57), although persistence of psychotic symptoms has been shown to occur despite adequate D_2 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-

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 therapeutic equivalence 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 monotherapy 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 D_2 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 D_2 and 5-HT_2 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. Wassef 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, Metrozole, 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-

dal symptoms (212,213). Recently, Volavka and colleagues (74) preliminarily reported a prospective double-blind randomized study, comparing the effects of clozapine, olanzapine, risperidone, and haloperidol, for 14 weeks in 157 treatment-resistant inpatients. Clozapine (mean dose 527 mg per day) and olanzapine (mean dose 30 mg per day), but not risperidone (mean dose 12 mg per day), demonstrated significantly greater efficacy than haloperidol (mean dose 26 mg per day) in reducing negative symptoms (74). However, it is debated whether clozapine's established efficacy for negative symptoms extends to the treatment of primary negative symptoms of the deficit syndrome (153,154,214). Few data are available from controlled trials to guide treatment of negative symptoms that persist despite optimal treatment with atypical agents (215). Clinicians commonly employ augmentation strategies, but evidence supporting this practice is derived mostly from an older literature describing combinations of augmenting agents added to conventional agents.

Adjunctive Agents

Following clozapine's example as an antagonist of D_2 and 5-HT_2 receptors, investigators combined haloperidol with ritanserin, a relatively selective 5-HT_{2A} and 5-HT_{1C} 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-HT_2 blockade may improve negative symptoms by enhancing mesocortical dopamine release. Svensson and colleagues demonstrated that 5-HT_2 blockade increases firing of midbrain dopamine neurons and reverses the effects of *N*-methyl-D-aspartate (NMDA) antagonism (217) and hypofrontality (218) on A10 dopamine neuronal firing. Because the available atypical agents achieve maximal occupation of 5-HT_2 receptors at usual therapeutic doses (57), it is unlikely that augmentation with 5-HT_2 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 D_1 receptor density after 6 months (273); treatment with a D_1 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 D_4 receptor antagonists may be potential novel antipsychotic drugs. Clozapine has a relatively higher affinity for the D_4 versus D_2 or D_3 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 D_4 receptors has been reported in the brains of patients with schizophrenia (292). Furthermore, the D_4 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 D_4 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 D_4 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 D_4 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 D_4 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 D_2-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 significant activation of heteroreceptors on target cells (300). Such partial dopamine agonists are therefore proposed to act as dopaminergic "buffers," reducing dopaminergic transmission without completely blocking it when dopaminergic activity is excessive, or conversely, stimulating it when it is reduced (7,299).

Despite the numerous compounds that were developed as partial agonists, none has proved to be sufficiently effective to warrant its full development and introduction for clinical use. The first of this class to show consistent and robust efficacy comparable to clinically used antipsychotic drugs, both conventional and atypical, is aripiprazole (301). Aripiprazole (OPC-14597) is a dual dopamine autoreceptor partial agonist and postsynaptic D_2 receptor antagonist (302,303). It has a modest affinity for 5-HT_2 receptors, but no appreciable affinity for D_1 receptors (304) (Table 56.1). Aripiprazole decreased striatal dopamine release (303), and inhibited the activity of dopamine neurons when applied locally to the ventral tegmental area in rats (305). Animal behavioral studies showed that the compound exhibited weak cataleptogenic effects compared to haloperidol and chlorpromazine despite the fact it has almost identical D_2 receptor antagonistic activity (302). The potency of aripiprazole to up-regulate striatal D_2 receptors in response to chronic treatment was much smaller than that of haloperidol, suggesting lower potential for EPS, including tardive dyskinesia (31). Aripiprazole is currently going through worldwide Phase III development. Preliminary clinical studies have shown its efficacy in alleviating both positive and negative symptoms of schizophrenia. Although current dogma suggests that such a D_2-selective agent would cause profound EPS and high sustained prolactin elevation, neither side effect has been seen clinically (306–308). Based on available data, it would appear that aripiprazole is the first compound with partial D_2 agonist properties to be a clinically effective antipsychotic agent. It has been proposed that aripiprazole induces "functionally selective" activation of D_2 receptors coupled to diverse G proteins (and hence different functions), thereby explaining its unique clinical effects (304).

CI-1007 is a new dopamine autoreceptor agonist and partial dopamine D_2/D_3 receptor agonist that is currently under development for the treatment of schizophrenia (309, 310). In preclinical studies, CI-1007 demonstrated that it inhibited the firing of dopamine neurons and reduced the synthesis, metabolism, utilization, and release of dopamine in the brain (310). In addition, it produced behavioral effects predictive of antipsychotic efficacy and indicated a low liability for EPS and TD (311).

5-HT Agents

The 5-HT_{2A} receptor subtype has received considerable attention because of its potential roles in the therapeutic action of atypical antipsychotic drugs (21,312); it is involved

in perception, mood regulation, and motor control (313). Available evidence indicates that 5-HT_{2A} 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-HT_{2A} 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-HT_{2A} 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-HT_{1A} receptors may contribute to its therapeutic action (313,327). Preclinical studies have suggested that serotonin 5-HT_{1A} agonists may potentiate the antipsychotic activity of dopaminergic antagonists (328). Activation of inhibitory 5-HT_{1A} autoreceptors may also counteract the induction of EPS owing to striatal D_2 receptor blockade (329). Further, in schizophrenic patients, increased 5-HT_{1A} receptor binding was seen in the prefrontal cortex (330,331). Based on these preclinical data, compounds that act as serotonin 5-HT_{1A} agonists are being developed as potential antipsychotic compounds.

S-16924 is a novel, potential antipsychotic agent with high affinity for dopamine $D_{2/4}$, α_1-adrenergic, and serotonin 5-HT_{2A} receptors, similar to that of clozapine, in addition to being a potent partial 5-HT_{1A} agonist (332). Reflecting its partial agonist actions at 5-HT_{1A} 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 antagonists 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 m_2/m_4 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 m_2 and m_4 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 D_1 and D_2 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 M_2/M_4 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 reproduce 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 noncompetitive 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 glycyldodecylamide 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, Ca^{2+}-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-methy-isoxazole-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 antimanic 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 neuroplastic 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 antimanic efficacy. In a pilot study, they found marked antimanic 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 antimanic agents for the treatment of bipolar disorder, and deserve further study in psychotic 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 D_2 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 s_1 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 s_1-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-

phrenia 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_2 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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REFERENCES

1. Lieberman JA. Atypical antipsychotic drugs as a first-line treatment of schizophrenia: a rationale and hypothesis. *J Clin Psychiatry* 1996;57(Suppl 11):68–71.
2. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A metaanalysis of randomized controlled trials. *Schizophr Res* 1999;35:51–68.
3. Miyamoto S, Duncan GE, Mailman RB, et al. Developing novel antipsychotic drugs: strategies and goals. *Curr Opin CPNS Invest Drugs* 2000;2:25–39.
4. Seeman P. Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. *Neuropsychopharmacology* 1992;7:261–284.
5. Kane JM. The current status of neuroleptic therapy. *J Clin Psychiatry* 1989;50:322–328.
6. Meltzer HY. Outcome in schizophrenia: beyond symptom reduction. *J Clin Psychiatry* 1999;60(Suppl 3):3–7.
7. Fleischhacker WW. New drugs for the treatment of schizophrenic patients. *Acta Psychiatr Scand (Suppl)* 1995;388:24–30.
8. Campbell M, Young PI, Bateman DN, et al. The use of atypical antipsychotics in the management of schizophrenia. *Br J Clin Pharmacol* 1999;47:13–22.
9. Meyer JM, Simpson GM. From chlorpromazine to olanzapine: a brief history of antipsychotics. *Psychiatr Serv* 1997;48:1137–1139.
10. Lieberman JA, Kane JM, Johns CA. Clozapine: guidelines for clinical management. *J Clin Psychiatry* 1989;50:329–338.
11. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45:789–796.
12. Lieberman JA. Understanding the mechanism of action of atypical antipsychotic drugs: a review of compounds in use and development. *Br J Psychiatry* 1993;163:7–18.
13. Duncan GE, Zorn S, Lieberman JA. Mechanisms of typical and atypical antipsychotic drug action in relation to dopamine and NMDA receptor hypofunction hypotheses of schizophrenia. *Mol Psychiatry* 1999;4:418–428.
14. Baldessarini RJ, Katz B, Cotton P. Dissimilar dosing with high-potency and low-potency neuroleptics. *Am J Psychiatry* 1984;141:748–752.
15. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992;49:538–544.
16. Kapur S, Remington G, Jones C, et al. High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* 1996;153:948–950.
17. Nordstrom AL, Farde L, Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry* 1993;33:227–235.
18. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D_2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000;157:514–520.
19. Remington G, Kapur S. D2 and 5-HT2 receptor effects of antipsychotics: bridging basic and clinical findings using PET. *J Clin Psychiatry* 1999;60(Suppl 10):15–19.
20. Nyberg S, Farde L. Non-equipotent doses partly explain differences among antipsychotics—implications of PET studies. *Psychopharmacology* 2000;148:22–23.
21. Lieberman JA, Mailman RB, Duncan G, et al. Serotonergic basis of antipsychotic drug effects in schizophrenia. *Biol Psychiatry* 1998;44:1099–1117.
22. Dragunow M, Robertson GS, Faull RL, et al. D2 dopamine receptor antagonists induce fos and related proteins in rat striatal neurons. *Neuroscience* 1990;37:287–294.
23. Robertson GS, Fibiger HC. Neuroleptics increase c-fos expression in the forebrain: contrasting effects of haloperidol and clozapine. *Neuroscience* 1992;46:315–328.

24. Merchant KM, Dorsa DM. Differential induction of neurotensin and c-fos gene expression by typical versus atypical antipsychotics. *Proc Natl Acad Sci USA* 1993;90:3447–3451.
25. Semba J, Sakai M, Miyoshi R, et al. Differential expression of c-fos mRNA in rat prefrontal cortex, striatum, *N. accumbens,* and lateral septum after typical and atypical antipsychotics: an in situ hybridization study. *Neurochem Int* 1996;29:435–442.
26. Deutch AY, Lee MC, Iadarola MJ. Regionally specific effects of atypical antipsychotic drugs on striatal Fos expression: the nucleus accumbens shell as a locus of antipsychotic action. *Mol Cell Neurosci* 1992;3:332–341.
27. Robertson GS, Matsumura H, Fibiger HC. Induction patterns of neuroleptic-induced Fos-like immunoreactivity as predictors of atypical antipsychotic activity. *J Pharmacol Exp Ther* 1994; 271:1058–1066.
28. Nakahara T, Kuroki T, Hashimoto K, et al. Effect of atypical antipsychotics on phencyclidine-induced expression of arc in rat brain. *Neuroreport* 2000;11:551–555.
29. Buckland PR, O'Donovan MC, McGuffin P. Both splicing variants of the dopamine D2 receptor mRNA are up-regulated by antipsychotic drugs. *Neurosci Lett* 1993;150:25–28.
30. Rogue P, Hanauer A, Zwiller J, et al. Up-regulation of dopamine D2 receptor mRNA in rat striatum by chronic neuroleptic treatment. *Eur J Pharmacol* 1991;207:165–168.
31. Inoue A, Miki S, Seto M, et al. Aripiprazole, a novel antipsychotic drug, inhibits quinpirole-evoked GTPase activity but does not up-regulate dopamine D2 receptor following repeated treatment in the rat striatum. *Eur J Pharmacol* 1997;321: 105–111.
32. Chakos MH, Lieberman JA, Bilder RM, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry* 1994;151:1430–1436.
33. Corson PW, Nopoulos P, Miller DD, et al. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *Am J Psychiatry* 1999;156: 1200–1204.
34. Chakos MH, Shirakawa O, Lieberman J, et al. Striatal enlargement in rats chronically treated with neuroleptic. *Biol Psychiatry* 1998;44:675–684.
35. Hawkins KA, Mohamed S, Woods SW. Will the novel antipsychotics significantly ameliorate neuropsychological deficits and improve adaptive functioning in schizophrenia? *Psychol Med* 1999;29:1–8.
36. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;153: 321–330.
37. Keefe RSE, Silva SG, Perkins DO, et al. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* 1999;25: 201–222.
38. Sharif ZA. Common treatment goals of antipsychotics: acute treatment. *J Clin Psychiatry* 1998;59(Suppl 19):5–8.
39. Barnes TRE, McPhillips MA. Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics. *Br J Psychiatry* 1999;174(Suppl 38):34–43.
40. Chakos MH, Mayerhoff DI, Loebel AD, et al. Incidence and correlates of acute extrapyramidal symptoms in first-episode of schizophrenia. *Psychopharmacol Bull* 1992;28:81–86.
41. Kane J. Olanzapine in the long-term treatment of schizophrenia. *Br J Psychiatry* 1999;174:26–29.
42. Fleischhacker WW, Hummer M. Drug treatment of schizophrenia in the 1990s. Achievements and future possibilities in optimising outcomes. *Drugs* 1997;53:915–929.
43. Ayuso-Gutierrez JL, del R, V. Factors influencing relapse in the long-term course of schizophrenia. *Schizophr Res* 1997;28: 199–206.
44. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophr Bull* 1995;21:419–429.
45. Revicki DA. Pharmacoeconomic studies of atypical antipsychotic drugs for the treatment of schizophrenia. *Schizophr Res* 1999;35:S101–S109
46. Weiden P, Aquila R, Standard J. Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J Clin Psychiatry* 1996; 57(Suppl 11):53–60.
47. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D1, D2 and Serotonin2 pKi values. *J Pharmacol Exp Ther* 1989;251: 238–246.
48. Gerlach J. New antipsychotics: classification, efficacy, and adverse effects. *Schizophr Bull* 1991;17:289–309.
49. Litman RE, Su TP, Potter WZ, et al. Idazoxan and response to typical neuroleptics in treatment-resistant schizophrenia. Comparison with the atypical neuroleptic, clozapine. *Br J Psychiatry* 1996;168:571–579.
50. Friedman JI, Temporini H, Davis KL. Pharmacologic strategies for augmenting cognitive performance in schizophrenia. *Biol Psychiatry* 1999;45:1–16.
51. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14:87–96.
52. Bymaster FP, Rasmussen K, Calligaro DO, et al. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. *J Clin Psychiatry* 1997;58(Suppl 10):28–36.
53. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics. Part I: pharmacology, pharmacokinetics, and efficacy. *Ann Pharmacother* 1999;33:73–85.
54. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 2000;57: 553–559.
55. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacologic characteristics? A review of the evidence. *Neuropsychopharmacology* 1998;18:63–101.
56. Kapur S, Zipursky RB, Remington G, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry* 1998;155:921–928.
57. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 1999;156:286–293.
58. Nordstrom AL, Farde L, Nyberg S, et al. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. *Am J Psychiatry* 1995;152:1444–1449.
59. Seeman P, Tallerico T. Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. *Mol Psychiatry* 1998;3:123–134.
60. Farde L, Nyberg S, Oxenstierna G, et al. Positron emission tomography studies on D2 and 5-HT2 receptor binding in risperidone-treated schizophrenic patients. *J Clin Psychopharmacol* 1995;15:19S–23S.
61. Remington G, Kapur S. Atypical antipsychotics: are some more atypical than others? *Psychopharmacology* 2000;148:3–15.
62. Tollefson GD, Kuntz AJ. Review of recent clinical studies with olanzapine. *Br J Psychiatry* 1999;174:30–35.
63. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* 1997;17:407–418.
64. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and

symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 1998;55:250–258.
65. Conley RR, Mahmoud R, the Risperidone Study Group. Efficacy of risperidone vs olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder. *Int J Neuropsychopharmacol* 2000;3(Suppl 1):S151(P.01.219).
66. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1998;18:296–304.
67. Arato M, O'Connor R, Meltzer H, et al. Ziprasidone: efficacy in the prevention of relapse and in the long-term treatment of negative symptoms of chronic schizophrenia. 10th Annual Meeting of the ECNP. Austria, 1997.
68. Pickar D, Owen RR, Litman RE, et al. Clinical and biologic response to clozapine in patients with schizophrenia. Crossover comparison with fluphenazine. *Arch Gen Psychiatry* 1992;49: 345–353.
69. Bradford DW, Chakos MH, Sheitman BB, et al. Atypical antipsychotic drugs in treatment-refractory schizophrenia. *Psychiatr Ann* 1998;28:618.
70. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry* 1994;151:1744–1752.
71. Kurz M, Hummer M, Kurzthaler I, et al. Efficacy of medium-dose clozapine for treatment-resistant schizophrenia. *Am J Psychiatry* 1995;152:1690–1691.
72. Flynn SW, MacEwan GW, Altman S, et al. An open comparison of clozapine and risperidone in treatment-resistant schizophrenia. *Pharmacopsychiatry* 1998;31:25–29.
73. Breier AF, Malhotra AK, Su TP, et al. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *Am J Psychiatry* 1999; 156:294–298.
74. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in treatment-resistant patients with schizophrenia and schizoaffective disorder. 38th ACNP Annual Meeting. Acapulco, Mexico, 1999.
75. Bondolfi G, Dufour H, Patris M, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. The Risperidone Study Group. *Am J Psychiatry* 1998;155:499–504.
76. Breier A, Hamilton SH. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Biol Psychiatry* 1999;45:403–411.
77. Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *Am J Psychiatry* 1998;155:914–920.
78. Dawkins K, Lieberman JA, Lebowitz BD, et al. Antipsychotics: Past and future—National Institute of Mental Health Division of Services and Intervention Research Workshop, July 14, 1998. *Schizophr Bull* 1999;25:395–404.
79. Meltzer HY. Treatment of schizophrenia and spectrum disorders: pharmacotherapy, psychosocial treatments, and neurotransmitter interactions. *Biol Psychiatry* 1999;46:1321–1327.
80. Hummer M, Fleischhacker WW. Non-motor side effects of novel antipsychotics. *Curr Opin CPNS Invest Drugs* 2000;2: 45–51.
81. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999; 60:358–363.
82. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 1998;44: 778–783.
83. Alvir JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 1993;329:162–167.
84. Csernansky J, Okamoto A. Risperidone vs haloperidol for prevention of relapse in schizophrenia and schizoaffective disorders: a long-term double-blind comparison. The 10th Biennial Winter Workshop on Schizophrenia. Davos, Switzerland, 2000.
85. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. *J Clin Psychopharmacol* 1995;15:36S–44S.
86. Conley RR, Mahmoud R, the Risperidone Study Group. Risperidone vs olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder: safety comparisons. *Int J Neuropsychopharmacol* 2000;3(Suppl 1):S151 (P.01.218).
87. Tollefson GD, Beasley CMJ, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry* 1997;154:1248–1254.
88. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. *Arch Gen Psychiatry* 1997;54:549–557.
89. Stip E, Boisjoly H. Quetiapine: are we overreacting in our concern about cataracts (the beagle effect)? Can J Psychiatry 1999; 44:503.
90. Ferris P. Ziprasidone. *Curr Opin CPNS Invest Drugs* 2000;2: 58–70.
91. Essock SM, Hargreaves WA, Dohm FA, et al. Clozapine eligibility among state hospital patients. *Schizophr Bull* 1996;22: 15–25.
92. Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *N Engl J Med* 1997;337:809–815.
93. Addington DE, Jones B, Bloom D, et al. Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. *Clin Ther* 1993;15:917–926.
94. Guest JF, Hart WM, Cookson RF, et al. Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia. *Br J Med Econ* 1996;10:59–67.
95. Viale G, Mechling L, Maislin G, et al. Impact of risperidone on the use of mental health care resources. *Psychiatr Serv* 1997; 48:1153–1159.
96. Beasley CMJ, Tollefson GD, Tran PV. Efficacy of olanzapine: an overview of pivotal clinical trials. *J Clin Psychiatry* 1997; 58(Suppl 10):7–12.
97. Tran PV, Dellva MA, Tollefson GD, et al. Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. *Br J Psychiatry* 1998;172: 499–505.
98. Amin S. Cost-effectiveness of atypical antipsychotics in chronic schizophrenia. *Hosp Med* 1999;60:410–413.
99. Glazer WM, Johnstone BM. Pharmacoeconomic evaluation of antipsychotic therapy for schizophrenia. *J Clin Psychiatry* 1997; 58(Suppl 10):50–54.
100. Hamilton SH, Revicki DA, Edgell ET, et al. Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia. Results from a randomised clinical trial. *Pharmacoeconomics* 1999;15:469–480.
101. Palmer CS, Revicki DA, Genduso LA, et al. A cost-effectiveness clinical decision analysis model for schizophrenia. *Am J Manag Care* 1998;4:345–355.
102. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry* 1993;50:369–376.
103. Bilder RM, Goldman RS, Robinson D, et al. Neuropsychology

of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry* 2000;157:549–559.
104. Gupta S, Andreasen NC, Arndt S, et al. The Iowa Longitudinal Study of Recent Onset Psychosis: one-year follow-up of first-episode patients. *Schizophr Res* 1997;23:1–13.
105. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* 1991;48:739–745.
106. Kopala LC, Good KP, Honer WG. Extrapyramidal signs and clinical symptoms in first-episode schizophrenia: response to low-dose risperidone. *J Clin Psychopharmacol* 1997;17: 308–313.
107. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. *Am J Psychiatry* 1999;156:79–87.
108. Lieberman JA, Phillips M, Kong L, et al. Efficacy and safety of clozapine versus chlorpromazine in first-episode psychosis: results of a 52 week randomized double blind trial. 39th ACNP Annual Meeting. San Juan, Puerto Rico, 2000.
109. Lieberman J, Tohen M, McEvoy J, et al. Olanzapine versus haloperidol in the treatment of first-episode psychosis. 39th ACNP Annual Meeting. San Juan, Puerto Rico, 2000.
110. Loebel AD, Lieberman JA, Alvir JMJ, et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* 1992;149:1183–1188.
111. Craig TJ, Bromet EJ, Fennig S, et al. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *Am J Psychiatry* 2000;157: 60–66.
112. Ho BC, Andreasen NC, Flaum M, et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 2000;157:808–815.
113. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first-episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1999;156:544–549.
114. Falloon IR, Kydd RR, Coverdale JH, et al. Early detection and intervention for initial episodes of schizophrenia. *Schizophr Bull* 1996;22:271–282.
115. McGorry PD, Edwards J, Mihalopoulos C, et al. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull* 1996;22:305–326.
116. Yung AR, McGorry PD, McFarlane CA, et al. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull* 1996;22:283–303.
117. Haddock G, Morrison AP, Hopkins R, et al. Individual cognitive-behavioural interventions in early psychosis. *Br J Psychiatry (Suppl)* 1998;172:101–106.
118. Linszen D, Dingemans P, Van der Does JW, et al. Treatment, expressed emotion and relapse in recent onset schizophrenic disorders. *Psychol Med* 1996;26:333–342.
119. Nugter A, Dingemans P, Van der Does JW, et al. Family treatment, expressed emotion and relapse in recent onset schizophrenia. *Psychiatr Res* 1997;72:23–31.
120. Hogarty GE. Depot neuroleptics: the relevance of psychosocial factors—a United States perspective. *J Clin Psychiatry* 1984;45: 36–42.
121. Marder SR, Hubbard JW, Van Putten T, et al. Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications. *Psychopharmacology* 1989;98:433–439.
122. Marder SR, Van Putten T, Mintz J, et al. Low- and conventional-dose maintenance therapy with fluphenazine decanoate. Two-year outcome. *Arch Gen Psychiatry* 1987;44:518–521.
123. Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry* 1992;53:426–433.
124. Schooler NR, Keith SJ, Severe JB, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. *Arch Gen Psychiatry* 1997;54:453–463.
125. Carpenter WRJ, Buchanan RW, Kirkpatrick B, et al. Diazepam treatment of early signs of exacerbation in schizophrenia. *Am J Psychiatry* 1999;156:299–303.
126. Essock SM, Hargreaves WA, Covell NH, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacol Bull* 1996;32:683–697.
127. Steingard S, Allen M, Schooler NR. A study of the pharmacologic treatment of medication-compliant schizophrenics who relapse. *J Clin Psychiatry* 1994;55:470–472.
128. Conley RR, Love RC, Kelly DL, et al. Rehospitalization rates of patients recently discharged on a regimen of risperidone or clozapine. *Am J Psychiatry* 1999;156:863–868.
129. Dixon L, Adams C, Lucksted A. Update on family psychoeducation for schizophrenia. *Schizophr Bull* 2000;26:5–20.
130. Huxley NA, Rendall M, Sederer L. Psychosocial treatments in schizophrenia: a review of the past 20 years. *J Nerv Ment Dis* 2000;188:187–201.
131. McFarlane WR, Lukens E, Link B, et al. Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Arch Gen Psychiatry* 1995;52:679–687.
132. Penn DL, Mueser KT. Research update on the psychosocial treatment of schizophrenia. *Am J Psychiatry* 1996;153:607–617.
133. Stein LI, Test MA. Alternative to mental hospital treatment. I. Conceptual model, treatment program, and clinical evaluation. *Arch Gen Psychiatry* 1980;37:392–397.
134. Heinssen RK, Liberman RP, Kopelowicz A. Psychosocial skills training for schizophrenia: lessons from the laboratory. *Schizophr Bull* 2000;26:21–46.
135. Herz MI, Lamberti JS, Mintz J, et al. A program for relapse prevention in schizophrenia: a controlled study. *Arch Gen Psychiatry* 2000;57:277–283.
136. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv* 1998;49: 196–201.
137. Hoge SK, Appelbaum PS, Lawlor T, et al. A prospective, multicenter study of patients' refusal of antipsychotic medication. *Arch Gen Psychiatry* 1990;47:949–956.
138. Pristach CA, Smith CM. Medication compliance and substance abuse among schizophrenic patients. *Hosp Community Psychiatry* 1990;41:1345–1348.
139. Van Putten T. Why do schizophrenic patients refuse to take their drugs? *Arch Gen Psychiatry* 1974;31:67–72.
140. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med* 1983;13:177–183.
141. Adams SGJ, Howe JT. Predicting medication compliance in a psychotic population. *J Nerv Ment Dis* 1993;181:558–560.
142. Day JC, Kinderman P, Bentall R. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. *Acta Psychiatr Scand* 1998;97: 93–97.
143. Finn SE, Bailey JM, Schultz RT, et al. Subjective utility ratings of neuroleptics in treating schizophrenia. *Psychol Med* 1990;20: 843–848.
144. Larsen EB, Gerlach J. Subjective experience of treatment, side-effects, mental state and quality of life in chronic schizophrenic out-patients treated with depot neuroleptics. *Acta Psychiatr Scand* 1996;93:381–388.
145. Perkins DO. Adherence to antipsychotic medications. *J Clin Psychiatry* 1999;60(Suppl 21):25–30.
146. Kemp R, David A, Haywood P. Compliance therapy: an intervention targeting insight and treatment adherence in psychotic patients. *Behav Cogn Psychother* 1996;24:331–350.

147. Kemp R, Kirov G, Everitt B, et al. Randomised controlled trial of compliance therapy. 18-month follow-up. *Br J Psychiatry* 1998;172:413–419.
148. Cramer JA, Rosenheck R. Enhancing medication compliance for people with serious mental illness. *J Nerv Ment Dis* 1999; 187:53–55.
149. Meltzer HY. Defining treatment refractoriness in schizophrenia. *Schizophr Bull* 1990;16:563–565.
150. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a metaanalysis of the outcome literature. *Am J Psychiatry* 1994;151:1409–1416.
151. Wolkin A, Barouche F, Wolf AP, et al. Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. *Am J Psychiatry* 1989;146:905–908.
152. Meltzer HY. Clozapine: pattern of efficacy in treatment-resistant schizophrenia. In: Meltzer HY, ed. *Novel antipsychotic drugs.* New York: Raven, 1992:33–46.
153. Carpenter WTJ, Conley RR, Buchanan RW, et al. Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995;152:827–832.
154. Meltzer HY. Clozapine: is another view valid? *Am J Psychiatry* 1995;152:821–825.
155. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994;151:825–835.
156. Wirshing DA, Marshall BDJ, Green MF, et al. Risperidone in treatment-refractory schizophrenia. *Am J Psychiatry* 1999;156: 1374–1379.
157. Bouchard RH, Merette C, Pourcher E, et al. Longitudinal comparative study of risperidone and conventional neuroleptics for treating patients with schizophrenia. The Quebec Schizophrenia Study Group. *J Clin Psychopharmacol* 2000;20:295–304.
158. Conley RR, Tamminga CA, Kelly DL, et al. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. *Biol Psychiatry* 1999;46:73–77.
159. Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. *J Clin Psychiatry* 1996; 57:395–397.
160. Still DJ, Dorson PG, Crismon ML, et al. Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. *Psychiatr Serv* 1996;47:1382–1384.
161. Klieser E, Lehmann E, Kinzler E, et al. Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995;15: 45S–51S.
162. Miller DD. The clinical use of clozapine plasma concentrations in the management of treatment-refractory schizophrenia. *Ann Clin Psychiatry* 1996;8:99–109.
163. Conley R, Brecher M, Group ROS. Risperidone versus olanzapine in patients with schizophrenia or schizoaffective disorder. 11th ECNP Congress. Paris, France, 1998.
164. Wang PS, West JC, Tanielian T, et al. Recent patterns and predictors of antipsychotic medication regimens used to treat schizophrenia and other psychotic disorders. *Schizophr Bull* 2000;26:451–457.
165. Naber D, Holzbach R, Perro C, et al. Clinical management of clozapine patients in relation to efficacy and side-effects. *Br J Psychiatry Suppl* 1992;54–59.
166. Morera AL, Barreiro PJL. Risperidone and clozapine combination for the treatment of refractory schizophrenia. *Acta Psychiatr Scand* 1999;99:305–306.
167. Friedman J, Ault K, Powchik P. Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. *Biol Psychiatry* 1997;42:522–523.
168. Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry* 1997;171:569–573.
169. Chong SA, Remington G. Clozapine augmentation: safety and efficacy. *Schizophr Bull* 2000;26:421–440.
170. Carman JS, Bigelow LB, Wyatt RJ. Lithium combined with neuroleptics in chronic schizophrenic and schizoaffective patients. *J Clin Psychiatry* 1981;42:124–128.
171. Growe GA, Crayton JW, Klass DB, et al. Lithium in chronic schizophrenia. *Am J Psychiatry* 1979;136:454–455.
172. Small JG, Kellams JJ, Milstein V, et al. A placebo-controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. *Am J Psychiatry* 1975;132:1315–1317.
173. Schulz SC, Thompson PA, Jacobs M, et al. Lithium augmentation fails to reduce symptoms in poorly responsive schizophrenic outpatients. *J Clin Psychiatry* 1999;60:366–372.
174. Wilson WH. Addition of lithium to haloperidol in non-affective, antipsychotic non-responsive schizophrenia: a double blind, placebo controlled, parallel design clinical trial. *Psychopharmacology* 1993;111:359–366.
175. Christison GW, Kirch DG, Wyatt RJ. When symptoms persist: choosing among alternative somatic treatments for schizophrenia. *Schizophr Bull* 1991;17:217–245.
176. Hogarty GE, McEvoy JP, Ulrich RF, et al. Pharmacotherapy of impaired affect in recovering schizophrenic patients. *Arch Gen Psychiatry* 1995;52:29.
177. Luchins DJ. Carbamazepine in violent non-epileptic schizophrenics. *Psychopharmacol Bull* 1984;20:569–571.
178. Neppe VM. Carbamazepine as adjunctive treatment in nonepileptic chronic inpatients with EEG temporal lobe abnormalities. *J Clin Psychiatry* 1983;44:326–331.
179. Okuma T, Yamashita I, Takahashi R, et al. A double-blind study of adjunctive carbamazepine versus placebo on excited states of schizophrenic and schizoaffective disorders. *Acta Psychiatr Scand* 1989;80:250–259.
180. Goff D, Baldessarini R. Antipsychotics. In: Ciraulo D, Shader R, Greenblatt D, et al, eds. *Drug interactions in psychiatry,* first ed. Baltimore: Williams & Wilkins, 1995:129–174.
181. Arana GW, Goff DC, Friedman H, et al. Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? *Am J Psychiatry* 1986;143:650–651.
182. Wassef AA, Dott SG, Harris A, et al. Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000;20:357–361.
183. Ko GN, Korpi ER, Freed WJ, et al. Effect of valproic acid on behavior and plasma amino acid concentrations in chronic schizophrenic patients. *Biol Psychiatry* 1985;20:209–215.
184. Wassef AA, Dott SG, Harris A, et al. Critical review of GABAergic drugs in the treatment of schizophrenia. *J Clin Psychopharmacol* 1999;19:222–232.
185. Arana GW, Ornsteen ML, Kanter F, et al. The use of benzodiazepines for psychotic disorders: a literature review and preliminary clinical findings. *Psychopharmacol Bull* 1986;22:77–87.
186. Wolkowitz OM, Pickar D. Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. *Am J Psychiatry* 1991; 148:714–726.
187. Wolkowitz OM, Breier A, Doran A, et al. Alprazolam augmentation of the antipsychotic effects of fluphenazine in schizophrenic patients. Preliminary results. *Arch Gen Psychiatry* 1988; 45:664–671.
188. Fink M, Sackeim HA. Convulsive therapy in schizophrenia? *Schizophr Bull* 1996;22:27–39.
189. Baker AA, Bird G, Lavin NI, et al. ECT in schizophrenia. *J Ment Sci* 1960;106:1506–1511.
190. Kino FF, Thorpe FT. Electrical convulsion therapy in 500 selected psychotics. *J Ment Sci* 1946;92:138–145.

191. Zeifert M. Results obtained from the administration of 12,000 doses of Metrazol to mental patients. *Psychiat Quart* 1941;15: 772–778.
192. Abraham KR, Kulhara P. The efficacy of electroconvulsive therapy in the treatment of schizophrenia. A comparative study. *Br J Psychiatry* 1987;151:152–155.
193. Brandon S, Cowley P, McDonald C, et al. Leicester ECT trial: results in schizophrenia. *Br J Psychiatry* 1985;146:177–183.
194. Taylor P, Fleminger JJ. ECT for schizophrenia. *Lancet* 1980; 1:1380–1382.
195. Dodwell D, Goldberg D. A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. *Br J Psychiatry* 1989;154:635–639.
196. Herzberg F. Prognostic variables for electro-shock therapy. *J Gen Psychol* 1954;50:79–86.
197. Kalinowsky LB, Worthing HJ. Results with electric convulsant treatment in 200 cases of schizophrenia. *Psychiat Quart* 1943; 17:144–153.
198. Lowinger L, Huddleson JH. Outcome in dementia praecox under electro-shock therapy as related to mode of onset and to number of convulsions induced. *J Nerv Ment Dis* 1945;102: 243–246.
199. Landy DA. Combined use of clozapine and electroconvulsive therapy. *Convulsive Ther* 1991;7:218–221.
200. Safferman AZ, Munne R. Combining clozapine with ECT. *Convulsive Ther* 1992;8:141–143.
201. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. *Arch Gen Psychiatry* 1999;56:300–311.
202. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry* 1999;56:315–320.
203. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996;348:233–237.
204. Hoffman RE, Boutros NN, Hu S, et al. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet* 2000;355:1073–1075.
205. Garety PA, Fowler D, Kuipers E. Cognitive-behavioral therapy for medication-resistant symptoms. *Schizophr Bull* 2000;26: 73–86.
206. Garety PA, Kuipers L, Fowler D, et al. Cognitive behavioural therapy for drug-resistant psychosis. *Br J Med Psychol* 1994;67: 259–271.
207. Kuipers E, Garety P, Fowler D, et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. I: effects of the treatment phase. *Br J Psychiatry* 1997; 171:319–327.
208. Tarrier N, Beckett R, Harwood S, et al. A trial of two cognitive-behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenic patients: I. Outcome. *Br J Psychiatry* 1993;162:524–532.
209. Tarrier N, Yusupoff L, Kinney C, et al. Randomised controlled trial of intensive cognitive behaviour therapy for patients with chronic schizophrenia. *Br Med J* 1998;317:303–307.
210. Gould RA, Mueser KT, Bolten E, et al. Cognitive therapy for psychosis in schizophrenia: an effect size analysis. *Schizophr Res* 2001;48:335–342.
211. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997;58:538–546.
212. Moller HJ. Neuroleptic treatment of negative symptoms in schizophrenic patients. Efficacy problems and methodological difficulties. *Eur Neuropsychopharmacol* 1993;3:1–11.
213. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *Am J Psychiatry* 1997;154: 466–474.
214. Conley R, Gounaris C, Tamminga C. Clozapine response varies in deficit versus non-deficit schizophrenic subjects. *Biol Psychiatry* 1994;35:746–747.
215. Goff DC, Evins AE. Negative symptoms in schizophrenia: neurobiological models and treatment response. *Harv Rev Psychiatry* 1998;6:59–77.
216. Gelders YG. Thymosthenic agents, a novel approach in the treatment of schizophrenia. *Br J Psychiatry (Suppl)* 1989;33–36.
217. Svensson TH, Mathe JM, Andersson JL, et al. Mode of action of atypical neuroleptics in relation to the phencyclidine model of schizophrenia: role of 5-HT2 receptor and alpha 1-adrenoceptor antagonism. *J Clin Psychopharmacol* 1995;15:11S–18S.
218. Svensson TH, Tung CS, Grenhoff J. The 5-HT2 antagonist ritanserin blocks the effect of pre-frontal cortex inactivation on rat A10 dopamine neurons in vivo. *Acta Physiol Scand* 1989; 136:497–498.
219. Goff DC, Brotman AW, Waites M, et al. Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. *Am J Psychiatry* 1990;147:492–494.
220. Evins A, Goff D. Adjunctive antidepressant drug therapies in the treatment of negative symptoms of schizophrenia. *CNS Drugs* 1996;6:130–147.
221. Goff DC, Midha KK, Sarid-Segal O, et al. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. *Psychopharmacology* 1995;117:417–423.
222. Lee MS, Kim YK, Lee SK, et al. A double-blind study of adjunctive sertraline in haloperidol-stabilized patients with chronic schizophrenia. *J Clin Psychopharmacol* 1998;18:399–403.
223. Buchanan RW, Kirkpatrick B, Bryant N, et al. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. *Am J Psychiatry* 1996;153:1625–1627.
224. McEvoy JP. The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs. *J Clin Psychopharmacol* 1983;3:288–302.
225. Tandon R, Greden JF, Silk KR. Treatment of negative schizophrenic symptoms with trihexyphenidyl. *J Clin Psychopharmacol* 1988;8:212–215.
226. Gerlach J, Rasmussen PT, Hansen L, et al. Antiparkinsonian agents and long-term neuroleptic treatment. Effect of G 31.406, orphenadrine, and placebo on parkinsonism, schizophrenic symptoms, depression and anxiety. *Acta Psychiatr Scand* 1977; 55:251–260.
227. Goff DC, Arana GW, Greenblatt DJ, et al. The effect of benztropine on haloperidol-induced dystonia, clinical efficacy and pharmacokinetics: a prospective, double-blind trial. *J Clin Psychopharmacol* 1991;11:106–112.
228. Johnstone EC, Crow TJ, Ferrier IN, et al. Adverse effects of anticholinergic medication on positive schizophrenic symptoms. *Psychol Med* 1983;13:513–527.
229. Tandon R, Greden JF. Cholinergic hyperactivity and negative schizophrenic symptoms. A model of cholinergic/dopaminergic interactions in schizophrenia. *Arch Gen Psychiatry* 1989;46: 745–753.
230. Tandon R, Mann NA, Eisner WH, et al. Effect of anticholinergic medication on positive and negative symptoms in medication-free schizophrenic patients. *Psychiatr Res* 1990;31: 235–241.
231. Goff DC, Amico E, Dreyfuss D, et al. A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994;151:429–431.
232. Baker LA, Cheng LY, Amara IB. The withdrawal of benztropine

mesylate in chronic schizophrenic patients. *Br J Psychiatry* 1983; 143:584–590.
233. Strauss ME, Reynolds KS, Jayaram G, et al. Effects of anticholinergic medication on memory in schizophrenia. *Schizophr Res* 1990;3:127–129.
234. Mathew RJ, Wilson WH. Changes in cerebral blood flow and mental state after amphetamine challenge in schizophrenic patients. *Neuropsychobiology* 1989;21:117–123.
235. Sanfilipo M, Wolkin A, Angrist B, et al. Amphetamine and negative symptoms of schizophrenia. *Psychopharmacology* 1996; 123:211–214.
236. Van Kammen DP, Boronow JJ. Dextro-amphetamine diminishes negative symptoms in schizophrenia. *Int Clin Psychopharmacol* 1988;3:111–121.
237. Wolkin A, Angrist B, Wolf A, et al. Effects of amphetamine on local cerebral metabolism in normal and schizophrenic subjects as determined by positron emission tomography. *Psychopharmacology* 1987;92:241–246.
238. Casey JF, Hollister LE, Klett CJ, et al. Combined drug therapy of chronic schizophrenics: controlled evaluation of placebo, dexto-amphetamine, imipramine, isocarboxazid and trifluoperazine added to maintenance doses of chlorpromazine. *Am J Psychiatry* 1961;117:997–1003.
239. Goff DC. Glutamate receptors in schizophrenia and antipsychotic drugs. In: Lidow MS, ed. *Neurotransmitter receptors in actions of antipsychotic medications.* New York: CRC Press, 2000: 121–136.
240. Goff DC, Tsai G, Levitt J, et al. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. *Arch Gen Psychiatry* 1999;56:21–27.
241. Heresco-Levy U, Javitt DC, Ermilov M, et al. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. *Arch Gen Psychiatry* 1999;56:29–36.
242. Tsai GE, Yang P, Chung LC, et al. D-serine added to clozapine for the treatment of schizophrenia. *Am J Psychiatry* 1999;156: 1822–1825.
243. Evins AE, Fitzgerald SM, Wine L, et al. Placebo-controlled trial of glycine added to clozapine in schizophrenia. *Am J Psychiatry* 2000;157:826–828.
244. Goff DC, Henderson DC, Evins AE, et al. A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. *Biol Psychiatry* 1999;45:512–514.
245. Potkin SG, Jin Y, Bunney BG, et al. Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. *Am J Psychiatry* 1999;156:145–147.
246. Kopelowicz A, Liberman RP, Mintz J, et al. Comparison of efficacy of social skills training for deficit and nondeficit negative symptoms in schizophrenia. *Am J Psychiatry* 1997;154: 424–425.
247. Cook JA, Razzano L. Vocational rehabilitation for persons with schizophrenia: recent research and implications for practice. *Schizophr Bull* 2000;26:87–103.
248. Birchwood M, Mason R, MacMillan F, et al. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. *Psychol Med* 1993;23:387–395.
249. Roy A, Thompson R, Kennedy S. Depression in chronic schizophrenia. *Br J Psychiatry* 1983;142:465–470.
250. Tollefson GD, Andersen SW, Tran PV. The course of depressive symptoms in predicting relapse in schizophrenia: a double-blind, randomized comparison of olanzapine and risperidone. *Biol Psychiatry* 1999;46:365–373.
251. Wassink TH, Flaum M, Nopoulos P, et al. Prevalence of depressive symptoms early in the course of schizophrenia. *Am J Psychiatry* 1999;156:315–316.
252. Johnson DA. Studies of depressive symptoms in schizophrenia. *Br J Psychiatry* 1981;139:89–101.
253. Koreen AR, Siris SG, Chakos M, et al. Depression in first-episode schizophrenia. *Am J Psychiatry* 1993;150:1643–1648.
254. Siris SG. Diagnosis of secondary depression in schizophrenia: implications for DSM-IV. *Schizophr Bull* 1991;17:75–98.
255. Newcomer JW, Faustman WO, Yeh W, et al. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. *Psychiatr Res* 1990;31:243–250.
256. Prosser ES, Csernansky JG, Kaplan J, et al. Depression, parkinsonian symptoms, and negative symptoms in schizophrenics treated with neuroleptics. *J Nerv Ment Dis* 1987;175:100–105.
257. Knights A, Hirsch SR. "Revealed" depression and drug treatment for schizophrenia. *Arch Gen Psychiatry* 1981;38:806–811.
258. Kramer MS, Vogel WH, DiJohnson C, et al. Antidepressants in 'depressed' schizophrenic inpatients. A controlled trial. *Arch Gen Psychiatry* 1989;46:922–928.
259. Harrow M, Yonan CA, Sands JR, et al. Depression in schizophrenia: are neuroleptics, akinesia, or anhedonia involved? *Schizophr Bull* 1994;20:327–338.
260. Van Putten T, May RP. "Akinetic depression" in schizophrenia. *Arch Gen Psychiatry* 1978;35:1101–1107.
261. Kane J, Rifkin A, Quitkin F, et al. Extrapyramidal side effects with lithium treatment. *Am J Psychiatry* 1978;135:851–853.
262. Siris SG, Bermanzohn PC, Mason SE, et al. Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. *Arch Gen Psychiatry* 1994;51:109–115.
263. Siris SG, Morgan V, Fagerstrom R, et al. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Arch Gen Psychiatry* 1987;44:533–539.
264. Plasky P. Antidepressant usage in schizophrenia. *Schizophr Bull* 1991;17:649–657.
265. Siris SG, Bermanzohn PC, Gonzalez A, et al. The use of antidepressants for negative symptoms in a subset of schizophrenic patients. *Psychopharmacol Bull* 1991;27:331–335.
266. Mohamed S, Paulsen JS, O'Leary D, et al. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry* 1999;56:749–754.
267. Aleman A, Hijman R, de Haan EH, et al. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry* 1999;156: 1358–1366.
268. Gold S, Arndt S, Nopoulos P, et al. Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *Am J Psychiatry* 1999;156:1342–1348.
269. Harvey PD, Silverman JM, Mohs RC, et al. Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. *Biol Psychiatry* 1999;45:32–40.
270. Buchanan RW, Strauss ME, Kirkpatrick B, et al. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. *Arch Gen Psychiatry* 1994;51:804–811.
271. Waddington JL, Youssef HA, Kinsella A. Cognitive dysfunction in schizophrenia followed up over 5 years, and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychol Med* 1990;20:835–842.
272. King DJ. The effect of neuroleptics on cognitive and psychomotor function. *Br J Psychiatry* 1990;157:799–811.
273. Lidow MS, Elsworth JD, P.S. Down-regulation of the D1 and D5 dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs. *J Pharmacol Exp Ther* 1997;281:597–603.
274. Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science* 2000;287:2020–2022.
275. Saletu B, Grunberger J, Linzmayer L, et al. Comparative placebo-controlled pharmacodynamic studies with zotepine and

clozapine utilizing pharmaco-EEG and psychometry. *Pharmacopsychiatry* 1987;20:12–27.
276. Goldberg TE, Greenberg RD, Griffin SJ, et al. The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *Br J Psychiatry* 1993;162:43–48.
277. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 1999;25:233–255.
278. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Arch Gen Psychiatry* 2000;57:249–258.
279. Goff DC, Bagnell AL, Perlis RH. Glutamatergic strategies for cognitive impairment in schizophrenia. *Psychiatr Ann* 1999;29: 649–654.
280. Tsai G, Yang P, Chung LC, et al. D-Serine added to antipsychotics for the treatment of schizophrenia. *Biol Psychiatry* 1998; 44:1081–1089.
281. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994;51:199–214.
282. Malhotra AK, Pinals DA, Adler CM, et al. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology* 1997;17:141–150.
283. Staubli U, Rogers G, Lynch G. Facilitation of glutamate receptors enhances memory. *Proc Natl Acad Sci USA* 1994;91: 777–781.
284. Goff D, Berman I, Posever T, et al. A preliminary dose-escalation trial of CX 516 (ampakine) added to clozapine in schizophrenia. *Schizophr Res* 1999;36:280.
285. Cassidy JJ, Easton M, Capelli C, et al. Cognitive remediation of persons with severe and persistent mental illness. *Psychiat Quart* 1996;67:313–321.
286. Corrigan PW, Hirschbeck JN, Wolfe M. Memory and vigilance training to improve social perception in schizophrenia. *Schizophr Res* 1995;17:257–265.
287. Brenner H, Roder V, Hodel B, et al. *Integrated psychological therapy for schizophrenia patients.* Toronto: Hogrefe & Huber, 1994.
288. Spaulding WD, Reed D, Sullivan M, et al. Effects of cognitive treatment in psychiatric rehabilitation. *Schizophr Bull* 1999;25: 657–676.
289. Hogarty GE, Flesher S. Practice principles of cognitive enhancement therapy for schizophrenia. *Schizophr Bull* 1999;25: 693–708.
290. Hogarty GE, Flesher S. Developmental theory for a cognitive enhancement therapy of schizophrenia. *Schizophr Bull* 1999;25: 677–692.
291. Van Tol HH, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 1991;350:610–614.
292. Seeman P, Guan HC, Van Tol HH. Dopamine D4 receptors elevated in schizophrenia. *Nature* 1993;365:441–445.
293. Danysz W. Sonepiprazole. *Curr Opin CPNS Invest Drugs* 2000; 2:97–104.
294. Mansbach RS, Brooks EW, Sanner MA, et al. Selective dopamine D4 receptor antagonists reverse apomorphine-induced blockade of prepulse inhibition. *Psychopharmacology* 1998;135: 194–200.
295. Feldpausch DL, Needham LM, Stone MP, et al. The role of dopamine D4 receptor in the induction of behavioral sensitization to amphetamine and accompanying biochemical and molecular adaptations. *J Pharmacol Exp Ther* 1998;286:497–508.
296. Kramer MS, Last B, Getson A, et al. The effects of a selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. D4 Dopamine Antagonist Group. *Arch Gen Psychiatry* 1997;54:567–572.
297. Bristow LJ, Kramer MS, Kulagowski J, et al. Schizophrenia and L-745,870, a novel dopamine D4 receptor antagonist. *Trends Pharmacol Sci* 1997;18:186–188.
298. Mansbach RS, Brooks EW, Sanner MA, et al. Selective dopamine D4 receptor antagonists reverse apomorphine-induced blockade of prepulse inhibition. *Psychopharmacology* 1998;135: 194–200.
299. Coward D, Dixon K, Enz A, et al. Partial brain dopamine D_2 receptor agonists in the treatment of schizophrenia. *Psychopharmacol Bull* 1989;25:393–397.
300. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology* 1996;124:2–34.
301. Ozdemir V. Aripiprazole. *Curr Opin CPNS Invest Drugs* 2000; 2:105–111.
302. Kikuchi T, Tottori K, Uwahodo Y, et al. 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC–14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. *J Pharmacol Exp Ther* 1995;274:329–336.
303. Semba J, Watanabe A, Kito S, et al. Behavioural and neurochemical effects of OPC-14597, a novel antipsychotic drug, on dopaminergic mechanisms in rat brain. *Neuropharmacology* 1995;34:785–791.
304. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 1999;20:612–627.
305. Momiyama T, Amano T, Todo N, et al. Inhibition by a putative antipsychotic quinolinone derivative (OPC-14597) of dopaminergic neurons in the ventral tegmental area. *Eur J Pharmacol* 1996;310:1–8.
306. Toru M, Miura S, Kudo Y. Clinical experiences of OPC-14597, a dopamine autoreceptor agonist in schizophrenic patients. *Neuropsychopharmacology* 1994;10:122S.
307. Petrie JL, Saha AR, McEvoy JP. Acute and long-term efficacy and safety of aripiprazole: a new atypical antipsychotic. *Schizophr Res* 1998;29:155.
308. Saha AR, Petrie JL, Ali MW. Safety and efficacy profile of aripiprazole, a novel antipsychotic. *Schizophr Res* 1999;36:295.
309. Wright JL, Caprathe BW, Downing DM, et al. The discovery and structure-activity relationships of 1,2,3,6-tetrahydro-4-phenyl-1-[(arylcyclohexenyl)alkyl]pyridines. Dopamine autoreceptor agonists and potential antipsychotic agents. *J Med Chem* 1994;37:3523–3533.
310. Pugsley TA, Davis MD, Akunne HC, et al. Cl-1007, a dopamine partial agonist and potential antipsychotic agent. I. neurochemical effects. *J Pharmacol Exp Ther* 1995;274:898–911.
311. Meltzer LT, Christoffersen CL, Corbin AE, et al. CI-1007, a dopamine partial agonist and potential antipsychotic agent. II. Neurophysiological and behavioral effects. *J Pharmacol Exp Ther* 1995;274:912–920.
312. Schmidt CJ, Sorensen SM, Kehne JH, et al. The role of 5-HT2A receptors in antipsychotic activity. *Life Sci* 1995;56:2209–2222.
313. Meltzer HY. Pre-clinical pharmacology of atypical antipsychotic drugs: a selective review. *Br J Psychiatry (Suppl)* 1996;29:23–31.
314. Ugedo L, Grenhoff J, Svensson TH. Ritanserin, a 5-HT2 receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. *Psychopharmacology* 1989;98: 45–50.
315. Schmidt CJ, Fadayel GM, Sullivan CK, et al. 5-HT2 receptors

exert a state-dependent regulation of dopaminergic function: studies with MDL 100,907 and the amphetamine analogue, 3,4-methylenedioxymethamphetamine. *Eur J Pharmacol* 1992; 223:65–74.
316. O'Neill MF, Heron-Maxwell CL, Shaw G. 5-HT2 receptor antagonism reduces hyperactivity induced by amphetamine, cocaine, and MK-801 but not D1 agonist C-APB. *Pharmacol Biochem Behav* 1999;63:237–243.
317. Sorensen SM, Kehne JH, Fadayel GM, et al. Characterization of the 5-HT2 receptor antagonist MDL 100907 as a putative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. *J Pharmacol Exp Ther* 1993;266:684–691.
318. Arnt J. Differential effects of classical and newer antipsychotics on the hypermotility induced by two dose levels of D-amphetamine. *Eur J Pharmacol* 1995;283:55–62.
319. Maurel-Remy S, Bervoets K, Millan MJ. Blockade of phencyclidine-induced hyperlocomotion by clozapine and MDL 100,907 in rats reflects antagonism of 5-HT2A receptors. *Eur J Pharmacol* 1995;280:R9–11.
320. Gleason SD, Shannon HE. Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. *Psychopharmacology* 1997;129:79–84.
321. Carlsson ML, Martin P, Nilsson M, et al. The 5-HT2A receptor antagonist M100907 is more effective in counteracting NMDA antagonist- than dopamine agonist-induced hyperactivity in mice. *J Neural Transm* 1999;106:123–129.
322. Schmidt CJ, Fadayel GM. The selective 5-HT2A receptor antagonist, MDL 100,907, increases dopamine efflux in the prefrontal cortex of the rat. *Eur J Pharmacol* 1995;273:273–279.
323. Schmidt CJ, Fadayel GM. Regional effects of MK-801 on dopamine release effects of competitive NMDA or 5-HT2A receptor blocade. *J Pharmacol Exp Ther* 1996;277:1541–1549.
324. Varty GB, Bakshi VP, Geyer MA. M100907, a serotonin 5-HT2A receptor antagonist and putative antipsychotic, blocks dizocilpine-induced prepulse inhibition deficits in Sprague-Dawley and Wistar rats. *Neuropsychopharmacology* 1999;20: 311–321.
325. Wang RY, Liang X. M100907 and clozapine, but not haloperidol or raclopride, prevent phencyclidine-induced blockade of NMDA responses in pyramidal neurons of the rat medial prefrontal cortical slice. *Neuropsychopharmacology* 1998;19:74–85.
326. Carlsson A. Focusing on dopaminergic stabilizers and 5-HT2A receptor antagonists. *Curr Opin CPNS Invest Drugs* 2000;2: 22–24.
327. Newman-Tancredi A, Chaput C, Verriele L, et al. Clozapine is a partial agonist at cloned, human serotonin 5-HT1A receptors. *Neuropharmacology* 1996;35:119–121.
328. Evenden JL. Effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) after repeated administration on a conditioned avoidance response (CAR) in the rat. *Psychopharmacology* 1992; 109:134–144.
329. Lucas G, Bonhomme N, De Deurwaerdere P, et al. 8-OH-DPAT, a 5-HT1A agonist and ritanserin, a 5-HT2A/C antagonist, reverse haloperidol-induced catalepsy in rats independently of striatal dopamine release. *Psychopharmacology* 1997;131: 57–63.
330. Burnet PW, Eastwood SL, Harrison PJ. 5-HT1A and 5-HT2A receptor mRNAs and binding site densities are differentially altered in schizophrenia. *Neuropsychopharmacology* 1996;15: 442–455.
331. Simpson MD, Lubman DI, Slater P, et al. Autoradiography with [3H]8-OH-DPAT reveals increases in 5-HT(1A) receptors in ventral prefrontal cortex in schizophrenia. *Biol Psychiatry* 1996;39:919–928.
332. Millan MJ, Schreiber R, Dekeyne A, et al. S 16924 ((R)-2-[1-[2-(2,3-dihydro-benzo[1,4] dioxin-5-yloxy)-ethyl]-pyrrolidin-3yl]-1-(4-fluoro-phenyl)-ethanone), a novel, potential antipsychotic with marked serotonin (5-HT)1A agonist properties: II. Functional profile in comparison to clozapine and haloperidol. *J Pharmacol Exp Ther* 1998;286:1356–1373.
333. Millan MJ, Gobert A, Newman-Tancredi A, et al. S 16924 ((R)-2-[1-[2-(2,3-dihydro-benzo[1,4] dioxin-5-yloxy)-ethyl]-pyrrolidin-3yl]-1-(4-fluoro-phenyl)-ethanone), a novel, potential antipsychotic with marked serotonin (5-HT)1A agonist properties: I. Receptorial and neurochemical profile in comparison with clozapine and haloperidol. *J Pharmacol Exp Ther* 1998; 286:1341–1355.
334. Bengtsson HJ, Kullberg A, Millan MJ, et al. The role of 5-HT1A autoreceptors and alpha1-adrenoceptors in the modulation of 5-HT release—III. Clozapine and the novel putative antipsychotic S 16924. *Neuropharmacology* 1998;37:349–356.
335. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry* 1998;6:S64–S78.
336. Kaufer D, Cummings JL, Christine D. Differential neuropsychiatric symptom responses to tacrine in Alzheimer's disease: relationship to dementia severity. *J Neuropsychiatry Clin Neurosci* 1998;10:55–63.
337. Levy ML, Cummings JL, Kahn-Rose R. Neuropsychiatric symptoms and cholinergic therapy for Alzheimer's disease. *Gerontology* 1999;45(Suppl 1):15–22.
338. Tune LE, Sunderland T. New cholinergic therapies: treatment tools for the psychiatrist. *J Clin Psychiatry* 1998;59(Suppl 13): 31–35.
339. Bodick NC, Offen WW, Levey AI, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997;54:465–473.
340. Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn* 1995;28:240–258.
341. Bymaster FP, Shannon HE, Rasmussen K, et al. Potential role of muscarinic receptors in schizophrenia. *Life Sci* 1999;64: 527–534.
342. Sauerberg P, Jeppesen L, Olesen PH, et al. Muscarinic agonists with antipsychotic-like activity: structure-activity relationships of 1,2,5-thiadiazole analogues with functional dopamine antagonist activity. *J Med Chem* 1998;41:4378–4384.
343. Bymaster FP, Shannon HE, Rasmussen K, et al. Unexpected antipsychotic-like activity with the muscarinic receptor ligand (5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane. *Eur J Pharmacol* 1998;356:109–119.
344. Chiodo LA, Bunney BS. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. *J Neurosci* 1983;3: 1607–1619.
345. Skarsfeldt T. Differential effects of repeated administration of novel antipsychotic drugs on the activity of midbrain dopamine neurons in the rat. *Eur J Pharmacol* 1995;281:289–294.
346. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 1991;148:1301–1308.
347. Malhotra AK, Pinals DA, Weingartner H, et al. NMDA receptor function and human cognition. The effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 1996;14: 301–307.
348. Lahti AC, Holcomb HH, Medoff DR, et al. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport* 1995;6:869–872.
349. Lahti AC, Koffel B, LaPorte D, et al. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 1995;13:9–19.

350. Yenari MA, Bell TE, Kotake AN, et al. Dose escalation safety and tolerance study of the competitive NMDA antagonist selfotel (CGS 19755) in neurosurgery patients. *J Neuropharmacol* 1998;21:28–34.
351. Deutsch SI, Mastropaolo J, Schwartx BL, et al. A ''glutamatergic hypothesis'' of schizophrenia. Rationale for pharmacotherapy with glycine. *J Neuropharmacol* 1989;12:1–13.
352. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* 1995;52:998–1007.
353. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. *Harv Rev Psychiatry* 1996;3:241–253.
354. Duncan GE, Moy SS, Knapp DJ, et al. Metabolic mapping of the rat brain after subanesthetic doses of ketamine: potential relevance to schizophrenia. *Brain Res* 1998;787:181–190.
355. Duncan GE, Miyamoto S, Leipzig JN, et al. Comparison of brain metabolic activity patterns induced by ketamine, MK-801 and amphetamine in rats: support for NMDA receptor involvement in responses to subanesthetic dose of ketamine. *Brain Res* 1999;843:171–183.
356. Miyamoto S, Leipzig JN, Lieberman JA, et al. Effects of ketamine, MK-801, and amphetamine on regional brain 2-deoxyglucose uptake in freely moving mice. *Neuropsychopharmacology* 2000;22:400–412.
357. Duncan GE, Leipzig JN, Mailman RB, et al. Differential effects of clozapine and haloperidol on ketamine-induced brain metabolic activation. *Brain Res* 1998;812:65–75.
358. Duncan GE, Miyamoto S, Leipzig JN, et al. Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. *J Pharmacol Exp Ther* 2000;293:8–14.
359. Bakshi VP, Geyer MA. Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine. *Psychopharmacology* 1995;122:198–201.
360. Bakshi VP, Swerdlow NR, Geyer MA. Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. *J Pharmacol Exp Ther* 1994;271:787–794.
361. Corbett R, Camacho F, Woods AT, et al. Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. *Psychopharmacology* 1995;120:67–74.
362. Duncan GE, Sheitman BB, Lieberman JA. An integrated view of pathophysiological models of schizophrenia. *Brain Res* Rev 1999;29:250–264.
363. Leeson PD, Iversen LL. The glycine site on the NMDA receptor: structure-activity relationships and therapeutic potential. *J Med Chem* 1994;37:4053–4067.
364. Javitt DC, Sershen H, Hashim A, et al. Reversal of phencyclidine-induced hyperactivity by glycine and the glycine uptake inhibitor glycyldodecylamide. *Neuropsychopharmacology* 1997; 17:202–204.
365. Rosse RB, Theut SK, Banay-Schwartz M, et al. Glycine adjuvant therapy to conventional neuroleptic treatment in schizophrenia: an open-label, pilot study. *J Neuropharmacol* 1989;12:416–424.
366. Costa J, Khaled E, Sramek J, et al. An open trial of glycine as an adjunct to neuroleptics in chronic treatment-refractory schizophrenics. *J Clin Psychopharmacol* 1990;10:71–72.
367. Heresco-Levy U, Javitt DC, Ermilov M, et al. Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. *Br J Psychiatry* 1996;169: 610–617.
368. Javitt DC, Zylberman I, Zukin SR, et al. Amelioration of negative symptoms in schizophrenia by glycine. *Am J Psychiatry* 1994;151:1234–1236.
369. van Berckel BN, Hijman R, van der Linden JA, et al. Efficacy and tolerance of D-cycloserine in drug-free schizophrenic patients. *Biol Psychiatry* 1996;40:1298–1300.
370. Goff DC, Tsai G, Manoach DS, et al. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. *Am J Psychiatry* 1995;152:1213–1215.
371. Goff DC, Tsai G, Manoach DS, et al. D-cycloserine added to clozapine for patients with schizophrenia. *Am J Psychiatry* 1996; 153:1628–1630.
372. Hashimoto A, Oka T. Free D-aspartate and D-serine in the mammalian brain and periphery. *Prog Neurobiol* 1997;52: 325–353.
373. Wolosker H, Sheth KN, Takahashi M, et al. Purification of serine racemase: biosynthesis of the neuromodulator D-serine. *Proc Natl Acad Sci USA* 1999;96:721–725.
374. Bergeron R, Meyer TM, Coyle JT, et al. Modulation of N-methyl-D-aspartate receptor function by glycine transport. *Proc Natl Acad Sci USA* 1998;95:15730–15734.
375. Berger AJ, Dieudonne S, Ascher P. Glycine uptake governs glycine site occupancy at NMDA receptors of excitatory synapses. *J Neurophysiol* 1998;80:3336–3340.
376. Javitt DC, Frusciante M. Glycyldodecylamide, a phencyclidine behavioral antagonist, blocks cortical glycine uptake: implications for schizophrenia and substance abuse. *Psychopharmacology* 1997;129:96–98.
377. Moghaddam B, Adams B, Verman A, et al. Activation of glutamatergic neurotransmission by ketamine. A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997;17:2921–2927.
378. Grunze HC, Rainnie DG, Hasselmo ME, et al. NMDA-dependent modulation of CA1 local circuit inhibition. *J Neurosci* 1996;16:2034–2043.
379. Attwell PJ, Singh KN, Jane DE, et al. Anticonvulsant and glutamate release-inhibiting properties of the highly potent metabotropic glutamate receptor agonist (2S,2′R, 3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV). *Brain Res* 1998;805: 138–143.
380. Battaglia G, Monn JA, Schoepp DD. In vivo inhibition of veratridine-evoked release of striatal excitatory amino acids by the group II metabotropic glutamate receptor agonist LY354740 in rats. *Neurosci Lett* 1997;229:161–164.
381. Anand A, Charney DS, Oren DA, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Arch Gen Psychiatry* 2000;57:270–276.
382. Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* 1998;281:1349–1352.
383. Bubser M, Keseberg U, Notz PK, et al. Differential behavioral and neurochemical effects of competitive and non-competitive NMDA receptor antagonists in rats. *Eur J Pharmacol* 1992;229: 75–82.
384. Hauber W, Andersen R. The non-NMDA glutamate receptor antagonist GYKI 52466 counteracts locomotor stimulation and anticataleptic activity induced by the NMDA antagonist dizocilpine. *Naunyn Sch Arch Pharmacol* 1993;348:486–490.
385. Willins DL, Narayanan S, Wallace LJ, et al. The role of dopamine and AMPA/kainate receptors in the nucleus accumbens in the hypermotility response to MK801. *Pharmacol Biochem Behav* 1993;46:881–887.
386. Sharp JW, Petersen DL, Langford MT. DNQX inhibits phencyclidine (PCP) and ketamine induction of the hsp 70 heat shock gene in the rat cingulate and retrosplenial cortex. *Brain Res* 1995;687:114–124.
387. Hampson RE, Rogers G, Lynch G, et al. Facilitative effects of the ampakine CX516 on short-term memory in rats: correlations with hippocampal neuronal activity. *J Neurosci* 1998;18: 2748–2763.
388. Hampson RE, Rogers G, Lynch G, et al. Facilitative effects of

the ampakine CX516 on short-term memory in rats: enhancement of delayed-nonmatch-to-sample performance. *J Neurosci* 1998;18:2740–2747.
389. Johnson SA, Luu NT, Herbst TA, et al. Synergistic interactions between ampakines and antipsychotic drugs. *J Pharmacol Exp Ther* 1999;289:392–397.
390. Manji HK, Bebchuk JM, Moore GJ, et al. Modulation of CNS signal transduction pathways and gene expression by mood-stabilizing agents: therapeutic implications. *J Clin Psychiatry* 1999;60(Suppl 2):27–39.
391. Manji HK, Lenox RH. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry* 1999;46:1328–1351.
392. Bebchuk JM, Arfken CL, Dolan-Manji S, et al. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Arch Gen Psychiatry* 2000;57:95–97.
393. Seeman MV. Current outcome in schizophrenia: women vs men. *Acta Psychiatr Scand* 1986;73:609–617.
394. Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. *Schizophr Bull* 1988;14:39–55.
395. Lindamer LA, Lohr JB, Harris MJ, et al. Gender, estrogen, and schizophrenia. *Psychopharmacol Bull* 1997;33:221–228.
396. Hafner H, Maurer K, Loffler W, et al. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry* 1993;162:80–86.
397. Hallonquist JD, Seeman MV, Lang M, et al. Variation in symptom severity over the menstrual cycle of schizophrenics. *Biol Psychiatry* 1993;33:207–209.
398. Riecher-Rossler A, Hafner H, Dutsch-Strobel A, et al. Further evidence for a specific role of estradiol in schizophrenia? *Biol Psychiatry* 1994;36:492–494.
399. Hafner H, Behrens S, De Vry J, et al. An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. *Psychiatr Res* 1991; 38:125–134.
400. Maurice T, Phan VL, Urani A, et al. Neuroactive neurosteroids as endogenous effectors for the sigma1 (sigma1) receptor: pharmacologic evidence and therapeutic opportunities. *Jpn J Pharmacol* 1999;81:125–155.
401. Roberts E, Bologa L, Flood JF, et al. Effects of dehydroepiandrosterone and its sulfate on brain tissue in culture and on memory in mice. *Brain Res* 1987;406:357–362.
402. Bologa L, Sharma J, Roberts E. Dehydroepiandrosterone and its sulfated derivative reduce neuronal death and enhance astrocytic differentiation in brain cell cultures. *J Neurosci Res* 1987;17: 225–234.
403. Compagnone NA, Mellon SH. Dehydroepiandrosterone: a potential signalling molecule for neocortical organization during development. *Proc Natl Acad Sci USA* 1998;95:4678–4683.
404. Mao X, Barger SW. Neuroprotection by dehydroepiandrosterone-sulfate: role of an NFkappaB-like factor. *Neuroreport* 1998; 9:759–763.
405. Bastianetto S, Ramassamy C, Poirier J, et al. Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage. *Mol Brain Res* 1999;66:35–41.
406. Bergeron R, de Montigny C, Debonnel G. Potentiation of neuronal NMDA response induced by dehydroepiandrosterone and its suppression by progesterone: effects mediated via sigma receptors. *J Neurosci* 1996;16:1193–1202.
407. Debonnel G, Bergeron R, de Montigny C. Potentiation by dehydroepiandrosterone of the neuronal response to N-methyl-D-aspartate in the CA3 region of the rat dorsal hippocampus: an effect mediated via sigma receptors. *J Endocrinol (Suppl)* 1996;150:S33–S42.
408. Flood JF, Smith GE, Roberts E. Dehydroepiandrosterone and its sulfate enhance memory retention in mice. *Brain Res* 1988; 447:269–278.
409. Flood JF, Roberts E. Dehydroepiandrosterone sulfate improves memory in aging mice. *Brain Res* 1988;448:178–181.
410. Flood JF, Morley JE, Roberts E. Memory-enhancing effects in male mice of pregnenolone and steroids metabolically derived from it. *Proc Natl Acad Sci USA* 1992;89:1567–1571.
411. Reddy DS, Kulkarni SK. The effects of neurosteroids on acquisition and retention of a modified passive-avoidance learning task in mice. *Brain Res* 1998;791:108–116.
412. Maurice T, Junien JL, Privat A. Dehydroepiandrosterone sulfate attenuates dizocilpine-induced learning impairment in mice via sigma 1-receptors. Behav *Brain Res* 1997;83:159–164.
413. Tourney G, Erb JL. Temporal variations in androgens and stress hormones in control and schizophrenic subjects. *Biol Psychiatry* 1979;14:395–404.
414. Strauss EB, Sands DE, Robibson AM, et al. Use of dehydroisoandrosterone in psychiatric treatment: a preliminary survey. *Br Med J* 1952;64–66.
415. Sands DE. Further studies on endocrine treatment in adolescence and early adult life. *J Ment Sci* 1954;100:211–219.
416. Strauss EB, Stevenson WAH. Use of dehydroisoandrosterone in psychiatric practice. *J Neurol Neurosurg Psychiat* 1955;18: 137–144.
417. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 1999;156:646–649.
418. Horrobin DF. Schizophrenia as a prostaglandin deficiency disease. *Lancet* 1977;1:936–937.
419. Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. *Biol Psychiatry* 2000;47:8–21.
420. Horrobin DF, Ally AI, Karmali RA, et al. Prostaglandins and schizophrenia: further discussion of the evidence. *Psychol Med* 1978;8:43–48.
421. Horrobin DF. Schizophrenia as a membrane lipid disorder which is expressed throughout the body. *Prostaglandins Leukot Essent Fatty Acids* 1996;55:3–7.
422. Delion S, Chalon S, Guilloteau D, et al. Age-related changes in phospholipid fatty acid composition and monoaminergic neurotransmission in the hippocampus of rats fed a balanced or an n-3 polyunsaturated fatty acid-deficient diet. *J Lipid Res* 1997;38:680–689.
423. Delion S, Chalon S, Guilloteau D, et al. alpha-Linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. *J Neurochem* 1996;66:1582–1591.
424. Wainwright PE. Do essential fatty acids play a role in brain and behavioral development? *Neurosci Biobehav Rev* 1992;16: 193–205.
425. Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr Res* 1998;30:193–208.
426. Puri BK, Richardson AJ, Horrobin DF, et al. Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. *Int J Clin Pract* 2000;54:57–63.
427. Fenton WS, Boronow J, Dickerson F, et al. Randomized trial of supplemental EPA for residual symptoms of schizophrenia. *Biol Psychiatry* 2000;47:159S–160S.
428. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987; 44:660–669.

429. Thome J, Foley P, Riederer P. Neurotrophic factors and the maldevelopmental hypothesis of schizophrenic psychoses. *J Neural Transm* 1998;105:85–100.
430. Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and pathophysiological perspective. *Biol Psychiatry* 1999;46:729–739.
431. Stahl SM. When neurotrophic factors get on your nerves: therapy for neurodegenerative disorders. *J Clin Psychiatry* 1998;59: 277–278.
432. Riva MA, Molteni R, Tascedda F, et al. Selective modulation of fibroblast growth factor-2 expression in the rat brain by the atypical antipsychotic clozapine. *Neuropharmacology* 1999;38: 1075–1082.
433. Altar CA. Neurotrophins and depression. *Trends Pharmacol Sci* 1999;20:59–61.
434. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996;317:417–423.

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