Antipsychotic Agents and Bipolar Disorder

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Antipsychotic agents have been used commonly in the treatment of bipolar disorder. This article reviews the evolution of the use of antipsychotic agents and their role in the acute and maintenance treatment of bipolar disorder. The focus is on neuroleptic drugs, the atypical antipsychotic drugs (risperidone and clozapine), and two of the new atypical antipsychotic drugs that were recently approved.
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Antipsychotic drugs have been utilized for the management of patients with bipolar disorder for several decades. A number of alternative somatic treatments approaches have been reported for patients who do not respond well to or who are intolerant to lithium treatment.[1,2] Somatic treatments other than lithium reported to have a role in the management of bipolar disorder include neuroleptics, anticonvulsant agents (carbamazepine, valproate, lamotrigine, gabapentin), calcium channel blockers, antidepressants, cholinergic agents, adrenergic blockers, thyroid hormones, phototherapy, and electroconvulsive therapy.[1,2] Still, in spite of all these alternatives, a proportion of patients with bipolar disorder continue to fail or be intolerant to these agents. Recently, the search for new drugs for bipolar disorder has involved the serotonin-dopamine antagonist antipsychotic agents, clozapine and risperidone.[3–6]

The present article reviews the evolution of the use of antipsychotic agents and their role in the treatment of bipolar disorder, paying particular attention to studies on the use of these agents in the treatment of acute mania and bipolar depression and in the prevention of subsequent affective episodes. Because of the lack of controlled studies on the use of risperidone and clozapine in the treatment of bipolar disorder, case reports and retrospective and open-label studies will be included. Particular attention will be given to the current role of neuroleptic drugs, the possible role of the atypical antipsychotic drugs (risperidone and clozapine) in the treatment of bipolar disorder,[4] and the new atypical antipsychotic drugs that have been approved recently.

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ANTIPSYCHOTICS IN BIPOLAR DISORDER

Prior to the lithium era, the pharmacologic strategies for bipolar disorder primarily included neuroleptics and antidepressants. Antipsychotic agents have been used in the treatment of bipolar disorder for close to 40 years. The use of the neuroleptic drug chlorpromazine to control agitated states was introduced by Delay and Deniker in 1952.[7] Neuroleptic drugs then were found to be quite instrumental in reducing the mortality that occurred secondary to dehydration and exhaustion in many highly agitated patients, and that has been referred to as *lethal catatonia*.[8] Also, the introduction of chlorpromazine in the mid-1950s provided the vehicle for deinstitutionalization for patients with severe forms of mental illness.[9] The exact role of these drugs in the acute and maintenance phase of manic-depressive illness for a long period of time was cloudy due partly to the unclear diagnostic boundaries between schizophrenia and bipolar disorder. In the earlier literature, patients given a diagnosis of manic-depressive illness sometimes had psychotic depression or schizophrenia.[10] Diagnoses were most often established on the basis of clinical impression, as opposed to the use of structured clinical interviews. Similarly, for many years, the diagnostic criteria used by psychiatrists in various parts of the world differed.[11] The lack of a clear distinction between these two diagnostic groups was evident in the U.S.-U.K. diagnostic study, where it became evident that American psychiatrists, in contrast to their British counterparts, were most likely to overdiagnose schizophrenia for affective illness, thus possibly affecting true estimates of mania.[12]

According to recent population-based studies, the lifetime prevalence of bipolar disorder is between 0.8% and 1.6%.[13–15] In recent years, the prevalence of treated affective disorders appears to have increased.[15] Stoll et al.[16]

reported a shift in the diagnostic frequencies of schizophrenia and affective disorders in six North American psychiatric hospitals. In this study, the frequency of schizophrenia decreased from a peak of 27% in 1966 to 9% in 1989. At the same time, the incidence of diagnosed major affective disorders increased from 10% in 1972 to 44% in 1990. The increased frequency of major affective disorders and the decrease in the frequency of schizophrenia could be explained by the narrower definition of schizophrenia in the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*.[17] Other factors that explain the increased frequency of affective disorders may be attributed to true changes in the incidence of the disorders, or a treatment-oriented diagnostic bias, which occurs when clinicians bias their diagnosis toward categories in which new pharmacologic treatments have become available.

NEUROLEPTICS IN ACUTE MANIA

Neuroleptics Compared With Lithium

Neuroleptics are commonly used in the treatment of acute mania. While controlled studies have shown that neuroleptics are superior to placebo in the treatment of acute mania,[18–20] they may be less efficacious compared with lithium. Initial studies had shown a superior efficacy of chlorpromazine compared with lithium; however, a meta-analysis of five well-controlled, double-blind studies[21–25] by Janicak and colleagues (1992)[26] documented the efficacy of lithium over neuroleptics (responders: lithium 89% vs. neuroleptics 38%, p = .0003). Nevertheless, neuroleptics offer the advantage of a more rapid onset of action over lithium and may be at least equal to and probably superior to lithium in the initial control of increased psychomotor activity.[21,22,25,27–29] The initial differences in treatment response produced by lithium and chlorpromazine may be attributed to the varied diagnostic criteria[30] or perhaps the rating scales used to measure changes in symptomatology.[25]

Combined Use of Lithium and Neuroleptics

For many years lithium and neuroleptic drugs were used separately, perhaps as a result of the reports of serious neurotoxicity that occurred when they were combined.[31,32] Another possible explanation of why these drugs were not used together, at least initially, was the lack of studies available on their efficacy when given in combination. During the last several years, the concurrent use of neuroleptics and lithium has become common practice and is considered safe and efficacious.[26] However, for many years, it remained unclear whether the combination of lithium with neuroleptics was more efficacious than either alone. Two studies address this very important question. In the first study, Biederman and colleagues[33] compared lithium and haloperidol with lithium and placebo in the acute phase of schizoaffective illness in a 5-week double-blind study that had 18 patients in each arm. The authors reported a statistically significant difference in favor of lithium combined with haloperidol over lithium alone. In addition, no evidence of neurotoxicity with this combination was noted. In the second study, Small and colleagues,[34] in a placebo-controlled study, compared neuroleptics combined with lithium or placebo in 22 chronic schizophrenics, 7 of whom had schizoaffective illness. The authors noted that the response of the excited patients was better than that of the depressed subgroup. Also, as in the previous study, there were no reports of neurotoxicity with their combined use. In summary, these two small studies as well as others[29,35] and extensive clinical experience suggest that the combined use of lithium with neuroleptics is safe and that neurotoxicity with this combination of drugs is not a common occurrence.

If the decision is made to start a neuroleptic which one should be used? Is one class of neuroleptic drug superior to another in the treatment of acute mania? Three studies address this question.[25,36,37] One study[36] showed that thiothixene or chlorpromazine (given in bioequivalent doses) as adjuncts to lithium were equally efficacious in controlling acute mania. Similarly, Cookson and colleagues[37] found no difference between chlorpromazine and pimozide for the treatment of acute mania. In contrast, Shopsin and colleagues,[25] in a double-blind study of haloperidol in mania, found haloperidol to be as effective as lithium and superior to chlorpromazine. In summary, no convincing differences exist among the various classes of neuroleptics in terms of their efficacy in the treatment of acute mania. While many clinicians prefer to use low-potency over high-potency neuroleptics in patients who are extremely excited or agitated in the belief that their sedative properties would confer an additional benefit, no consistent data suggest that this is the case. Patients experiencing a first-episode of mania are more likely to be treated with neuroleptics of intermediate potency, perhaps because this population is more sensitive to the extrapyramidal side effects of higher-potency neuroleptics.[38] In the McLean/Harvard first-episode mania project,[39] the frequency of neuroleptic drugs prescribed by potency in 55 patients consecutively hospitalized for a first-episode of mania was intermediate-potency, 87%; high-potency, 13%; and low-potency, 4.3%.

A dose relationship for neuroleptic treatment in patients with schizophrenia is probably between 100 and 700 mg/day in chlorpromazine equivalents (mean 350 mg/day)[40] or between 1 and 12 mg/day of haloperidol (mean 7 mg/day).[41] In patients with acute mania, the doses of neuroleptics have not been systematically studied, but are probably in the same range as that previously described for schizophrenic patients. To our knowledge, only one study has examined the antimanic response to

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neuroleptic dose by using a fixed-dose strategy.[42] In this study, three doses—10, 30, or 80 mg/day—of haloperidol were compared under double-blind conditions for up to 6 weeks. The authors concluded that more than 10 mg/day of haloperidol offered no advantage in mania. Another study[36] found that moderate doses of either chlorpromazine or thiothixene as adjuncts to lithium were effective in the treatment of acute mania.

Four studies have reported the neuroleptic dosage in manic patients either during hospitalization or at discharge[39,43–45]; two of these studies report the neuroleptic doses at 6 months after discharge. In one study of multiple-episode patients,[43] the mean neuroleptic dosage at discharge in 26 manic patients treated primarily with lithium or valproate was 525 mg/day (chlorpromazine equivalent). Similarly, a second study[44] of multiple-episode patients showed that the mean neuroleptic dose (chlorpromazine equivalent) at discharge was 793 mg/day and at 6 months after discharge was 634 mg/day in 40 bipolar patients. In contrast, in the McLean/Harvard first-episode mania project,[39] patients never previously exposed to neuroleptics were treated with much lower doses of neuroleptics. The mean chlorpromazine-equivalent dose at discharge was 175 mg/day and at 6 months after discharge was 57 mg/day. Baldessarini and colleagues[45] observed that neuroleptic doses (chlorpromazine equivalents) in patients with major affective disorder were similar in 1989 and 1993 at McLean Hospital despite a decreased length of stay (290 vs. 274 mg/day). In summary, high dosages of neuroleptics are unlikely to be more effective over moderate doses of neuroleptics and may increase the risk of side effects.

Adverse Effects of Neuroleptics

It has been reported that patients with affective disorders and neuroleptic-naive patients may have increased vulnerability to extrapyramidal side effects[46] and tardive dyskinesia.[47] Data involving relatively young adult schizophrenics[48,49] suggest a cumulative incidence of tardive dyskinesia of 4% per year of neuroleptic exposure. In patients with affective disorders, the estimated cumulative incidence has been suggested to be twice as high.[50] One study[51] reports a higher frequency of neuroleptic-induced dystonia in manic (26.1%; 12 of 46 patients) than in schizophrenic patients (5.9%; 8 of 135 patients). Some authors have recommended the use of prophylactic anticholinergics in young men to prevent dystonic reactions.[52] If additional sedation is required to control agitation, nonneuroleptic agents (e.g., lorazepam, clonazepam) should be considered in order to minimize the total daily dose of neuroleptics.[53,54]

An important question is whether nonneuroleptic drugs are as effective as neuroleptics in combination with the mood-stabilizer for achieving behavioral control with a minimum risk of extrapyramidal symptoms. Recent studies suggest that benzodiazepines are equally efficacious as neuroleptic drugs in the treatment of acute mania. Lenox et al.[55] studied 20 hospitalized patients who met DSM-III-R criteria for bipolar disorder, manic, who were randomly assigned to receive either lorazepam or haloperidol concomitantly with lithium. The authors concluded that there were no differences in time to response and efficacy between the two groups.[55] Another recent study found that oral loading of divalproex was as efficacious and better tolerated than haloperidol in the treatment of acute psychotic mania. In this study,[56] 36 consecutive hospitalized patients with bipolar disorder, manic or mixed with psychotic features, were randomly assigned to receive either 20 mg/kg/day of divalproex or 0.2 mg/kg/day of haloperidol for 6 days without other psychotropic drugs except for lorazepam. The authors concluded that divalproex oral loading and haloperidol were equally effective in reducing acute psychotic mania with minimal side effects and, as expected, extrapyramidal symptoms were significantly more common with haloperidol.

Neuroleptics in Maintenance Treatment of Bipolar Disorder

The efficacy of neuroleptics as a maintenance treatment for bipolar patients has not been studied systematically, even though these drugs are commonly used in the long-term treatment of bipolar patients.[57] Most studies have examined the role of lithium and neuroleptics in acute episodes, but the place of this combination in maintenance treatment is less well documented.[58,59] Schou[60] found that one third of lithium-treated bipolar patients followed by a clinic were also maintained on neuroleptics. Maintenance treatment of bipolar disorder with antipsychotic medications is generally recommended after the patient has failed to respond to or tolerate either a single or a combination of mood stabilizers. Neuroleptic drugs are often avoided because of the behavioral and neurologic side effects associated with long-term treatment.[50,57] Undoubtedly, the mood stabilizers lithium, carbamazepine, and divalproex are effective both as antimanic agents and in preventing relapses.[1,2] However, many cases of bipolar disorder may not respond to the use of mood stabilizers alone and, in those cases, neuroleptics are often used as adjuncts. Little research supports the routine use of neuroleptics alone as a maintenance treatment of bipolar disorder. Continued use of neuroleptics may provide protection against recurrent mood elevation and psychotic symptoms, but it may not alter underlying cyclicity nor protect against recurrence of depression.[18] In fact, it has been suggested that the routine use of neuroleptics (i.e., to control manic symptoms) may precipitate major depressive episodes that often follow manic episodes[61,62] and induce rapid cycling in some patients.[61] In addition, patients with bipolar disorder may be at greater risk than patients with schizophrenia for developing tardive dyskinesia during neuroleptic treatment.[47,49,63] Furthermore, continuous use of neuroleptics

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in bipolar patients has been reported to interfere with long-term functioning.[64] It is commonly recommended that neuroleptic drugs be discontinued as soon as possible in bipolar patients in order to avoid the above complications.

However, several studies suggest that many patients remain on neuroleptic treatment. A recent review by Sernyak and Woods[65] reported marked variation in the extent of the use of neuroleptics in patients with manic-depressive illness. Yassa and colleagues[66] reported that 42 (61%) of 69 bipolar inpatients and outpatients maintained on lithium were also receiving neuroleptics. Mukherjee and colleagues[47] reported that 124 (95%) of 131 bipolar patients receive neuroleptics at some time during their illness. Waddington and Youssef[67] reported that 18 (72%) of 25 bipolar patients were receiving neuroleptics. Dinan and Kohen[68] found that in a group of 40 outpatients with bipolar disorder, all 40 (100%) had received neuroleptics for at least 2 months. Waddington and colleagues[69] reported that 44 (90%) of 49 bipolar outpatients had received neuroleptics at some time. Hunt and Silverstone[70] found that 68 (99%) of 69 patients had received neuroleptics for at least 3 months at some time during the previous 4 years; furthermore, 31 (45%) of the 69 patients had received neuroleptics continuously for at least 6 months. Janicak and colleagues[36] reported that 9 (31%) of 29 acutely manic patients had received neuroleptics in conjunction with lithium. In another survey[71] of 257 patients (215 with bipolar disorder, 42 with schizoaffective disorder), 94 patients (37%) were receiving maintenance antipsychotic treatment in addition to lithium and other agents. In a study conducted at McLean Hospital, 41 (55%) of 75 patients were receiving neuroleptics at discharge and 4 years later, a similar number (N = 33; 46%) continued on neuroleptic therapy.[64] Another study examined the use of neuroleptic drugs in a Scandinavian clinical setting.[72] The authors found that of 125 consecutively admitted manic patients, 111 (89%) were primarily treated with neuroleptics during the index episode, and a substantial use of drug combinations was observed.

The results of these pooled studies suggest that 592 (68%; range, 31%–100%) of 869 bipolar patients were receiving neuroleptics at some time during their illness. These results should be interpreted with caution as much variability exists in the different studies examined. Differences in results may be due to diagnostic criteria used, treatment settings from where patients were selected, phase of treatment patients were in (acute vs. continuation phase of bipolar disorder), and concomitant medications used. Some authors[43] suggest that the frequent use of neuroleptics in combination with lithium may result from the high number of involuntary admissions in the patients under study or, at least initially, that neuroleptics may be more effective than lithium in managing highly active manic patients, partly due to the relative slow onset of action of lithium.[27]

Three recent studies with a similar design permit a closer examination of the rates of neuroleptic use at discharge and 6-month follow-up.[38,44,73] In a retrospective study, Sernyak and colleagues[44] determined the neuroleptic use in 40 patients discharged on a combination of lithium and neuroleptics and found that at 6 months after discharge 38 (95%) were still taking neuroleptic drugs. In another study,[73] 52 (68%) of 77 patients were taking a neuroleptic drug both at discharge and at 6-month follow-up. Neither study focused on the first episode of mania. In the third study,[38] 46 (84%) of 55 first-episode manic patients were discharged on neuroleptic treatment, of whom only 17 (31%) were still taking them at 6-month follow-up. The difference between the first two studies compared to the first-episode study clearly suggests that first-episode patients are less likely to receive neuroleptics as maintenance treatment. Furthermore, neuroleptic-naive patients have been reported to be more sensitive to developing extrapyramidal symptoms during neuroleptic therapy, and are probably tapered off the drugs sooner than patients who have previously taken neuroleptics. The incidence of neuroleptic exposure at 6 months after discharge was higher in patients with a longer duration of psychiatric illness. The mean duration of psychiatric illness was 13 years in the first study[44] (95% of patients still taking neuroleptics at 6-month follow-up), 10 years in the second study[73] (68% of patients taking neuroleptics at 6-month follow-up), and < 1 year in the first-episode study[38] (31% of patients taking neuroleptics at 6-month follow-up). These combined results suggest that the more chronically ill bipolar patients are, the greater the risk of neuroleptic exposure will be. Multiple-episode bipolar patients remaining on neuroleptic therapy at follow-up probably represent a more chronically ill population for whom neuroleptics are used as adjuncts to other mood stabilizers in order to minimize the risk of relapse.

Recently Keck et al.[73] identified the factors associated with maintenance antipsychotic treatment in bipolar patients. Significant factors included male gender, medication noncompliance in the month prior to the index hospitalization, severity of manic symptoms, and being prescribed antipsychotic medications at time of discharge.

Depot Neuroleptics

The value of depot neuroleptics in the maintenance treatment of schizophrenic illness is well established. Janicak and colleagues[74] reviewed the literature of schizophrenic patients who relapsed while on oral or depot antipsychotic agents. A meta-analysis of six random-assignment, double-blind studies suggested a significantly lower relapse percentage on depot versus oral medication ($p = .0002$).[74] However, only a few studies have described their use in bipolar and schizoaffective disorder. Four open, mirror-design studies have examined the efficacy of depot neuroleptics as adjunctive treatment with lithium

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and/or carbamazepine.[75–78] In all four studies, the combination appeared to be effective in preventing relapses in patients who had predominantly manic or mixed state illnesses. In addition, two of these studies suggested that depot antipsychotics were effective in reducing the cycling in seven (78%) of nine rapid cycling patients.[77,78] Margakis[79] has also observed that depot medication can be used in those manic-depressive patients whose compliance with oral medication is unreliable and who are prone to hypomanic episodes.

Three open, prospective, comparative maintenance studies of depot flupentixol in patients with bipolar disorder have also been reported.[80–82] In the first of these studies, Kielholz and colleagues[80] compared flupentixol decanoate with lithium maintenance for up to 2 years in 30 patients with bipolar disorder and found that both were equally effective in preventing depressive and manic relapses. In the second study, Ahlfors and colleagues[81] compared the prophylactic effect of flupentixol against lithium for up to 3 years in 42 patients with bipolar disorder, and found that flupentixol was associated with significant decreases in the frequency and duration of manic episodes, but with significant increases in the duration and frequency of depressive episodes. In contrast, the third study by Esparon and colleagues[82] compared the addition of flupentixol to ongoing lithium treatment in a double-blind, crossover 2-year study of 15 patients with bipolar disorder and found that flupentixol did not have a prophylactic effect.

Neuroleptics and Bipolar Depression

In the late 1960s, flupentixol was reported to relieve moderate symptoms of acute depression[83,84]; however, these findings have not been replicated. Neuroleptics have been reported to be effective in combination with antidepressants in the treatment of unipolar or bipolar patients with psychotic depression[85,86] and in preventing depressive episodes. Hendrick et al.[87] described three patients with bipolar disorder who experienced depressive episodes after neuroleptic discontinuation. However, when the neuroleptic agent was reinstituted in these three patients, their depressive symptoms rapidly abated. In general, most studies examining the course of patients with bipolar disorder treated with neuroleptics suggest that they may be at an increased risk for depressive episodes.[61] Similarly, in the study performed by Ahlfors and colleagues,[81] the authors found that patients on the neuroleptic flupentixol were more likely than those taking lithium to have recurrent depression.

ATYPICAL ANTIPSYCHOTICS

Clinical experience accumulated over the last two decades indicates that about 40% of patients in the acute phase of bipolar disorder and close to 80% of patients with the mixed manic-depressive and rapid cycling forms of bipolar disorder are resistant to lithium.[88–90] Furthermore, a significant proportion of bipolar patients are unable to tolerate the side effects of lithium. The introduction of the anticonvulsants divalproex and carbamazepine for the treatment of bipolar disorders has been a significant advance, as they are effective not only in classic mania, but also in the rapid cycling and mixed forms of bipolar disorder where lithium is less effective.[2,89–91] However, in spite of these newer agents, some bipolar patients are still nonresponsive to mood-stabilizing drugs and require antipsychotic compounds. Neuroleptic drugs have been mainly used as a treatment for the psychotic symptoms present during one of the poles of the illness or as an adjunctive when other alternatives have failed,[50] but the use of neuroleptics in manic-depressive illness is limited because of their side effects, including akathisia, tardive dyskinesia, and neuroleptic malignant syndrome. The search for new drugs for bipolar disorder has recently involved the serotonin-dopamine antagonists clozapine and risperidone. The atypical antipsychotic drug clozapine has been reported to be effective in the treatment of not only patients with schizophrenia but also patients with schizoaffective and bipolar disorder, including those with treatment-resistant conditions.[4,5,92,93]

Risperidone in Bipolar Disorder

Because of risperidone's more favorable side effect profile compared with that of clozapine and standard antipsychotics,[94] several investigators examined its tolerability and efficacy in the treatment of schizoaffective and bipolar disorders. Hillert and colleagues[95] first reported that the novel antipsychotic drug risperidone may reduce psychotic and affective symptoms in patients with DSM-III-R major depression with psychotic features or schizoaffective disorder, depressive type. Following this open-label study, several other studies addressed the question of whether risperidone has a role in the treatment of affectively ill patients. Some suggest that risperidone may be effective as an adjunctive mood stabilizer in schizoaffective and bipolar patients[6,96–98]; and in depressive syndromes of severe mood disorders.[95,99,100] Singh and Catalen[101] reported on four patients with psychotic mania owing to HIV infection who had a mean 77% reduction in Young Mania Rating Scale (YMRS) scores over the course of 10 days (mean risperidone dose 2–4 mg/day). Another study also found positive results in HIV-related manic psychosis.[102] However, another study fails to support the efficacy of risperidone in schizoaffective bipolar patients.[103] In this study, all 5 manic patients discontinued risperidone secondary to adverse events, lack or response, or worsening of symptoms. However, most of these patients had taken their psychotropic medications within a short period of time before beginning risperidone. Furthermore, Dwight and colleagues,[98] as well as others,[95,99,104–107] suggest that risperidone may possess

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antidepressant activity and induce mania in some schizoaffective disorder bipolar type patients, especially those who are not receiving a concomitant mood stabilizer. Our group[5] conducted a 6-week open label study of risperidone and concurrent mood-stabilizing drugs in the treatment of DSM-III-R acute psychotic mania. Fifteen subjects were included; their mean age was 38 years old. Thirteen patients completed 2 weeks and 8 completed 6 weeks of treatment. By the second week of treatment, 8 patients (62%) had a 50% improvement in the Brief Psychiatric Rating Scale (BPRS) and by Week 6, 7 of the 8 subjects (88%) had a 50% improvement. The YMRS was also utilized. By Week 2, 10 (77%) of 13 patients had a 50% improvement, and by Week 6, 8 subjects (100%) had a 50% improvement. Importantly, no patient worsened. Risperidone dosages ranged from 2 to 6 mg/day with a mean of 3 mg/day.

It has been suggested that affectively ill patients may require lower doses than that recommended for the treatment of schizophrenia, possibly because higher doses of risperidone may be associated with more side effects in affectively ill patients.[100]

Only one study searched for predictors of response to risperidone in patients with schizoaffective and bipolar disorders.[99] In this study, Keck and colleagues, by way of a retrospective chart review, assessed the factors associated with risperidone response in 144 consecutive patients treated with the drug for at least 2 weeks. The authors found that patients displaying a moderate-to-marked response to risperidone were more likely to be younger; receive diagnoses of bipolar disorder or schizoaffective disorder, depressive type; and have a shorter duration of illness and shorter length of hospital stay prior to risperidone treatment.

Clozapine in Bipolar Disorder

A growing number of studies performed over the past decade have shown that clozapine, an atypical antipsychotic drug effective in treatment refractory schizophrenia,[108,109] appears to be effective for the acute and prophylactic treatment of some patients with schizoaffective and bipolar disorder who have responded inadequately to or are unable to tolerate lithium, carbamazepine, valproate, or conventional antipsychotic drugs.[92,93,110]

Clozapine has been shown in two open-label studies to be effective in treatment-refractory acute mania. In the first study, Calabrese and colleagues[110] examined the efficacy of clozapine in 25 acute manic patients with either bipolar disorder (N = 10) or schizoaffective disorder-bipolar subtype (N = 15) for over 13 weeks. Lithium, anticonvulsants, and neuroleptics had been ineffective, produced intolerable side effects, or both in these patients. Criteria for nonresponse included a 6-week or more trial of lithium with a plasma level of over 0.8 mEq/L, or carbamazepine at a plasma level of more than 6 mg/mL, or valproate at a plasma level over 50 mg/L. Patients also had to have failed to respond to at least two 6-week trials of neuroleptics at a dose equivalent to 20 mg/day of haloperidol. Of a total of 25 patients, 22 completed the 13-week trial. Eighteen (72%) patients of the 25 exhibited marked improvement on the YMRS, and 8 (32%) exhibited marked improvement on the BPRS. Patients with bipolar disorder had greater improvement compared to those with schizoaffective disorder. When assessed with the BPRS, non-rapid-cyclers did better than rapid cyclers. In this study, the most common adverse effects were hypersalivation in 88% of patients, followed by sedation in 46% of patients, dizziness in 36% of patients, and weight gain in 28% of the patients. This study suggests that clozapine is effective in treatment-resistant bipolar patients. Importantly, clozapine was effective in decreasing not only psychotic symptoms, but manic symptoms as well. Our group conducted another trial in treatment-resistant patients (Zarate CA, Tohen M. 1997. Unpublished data). A total of 22 patients with refractory acute mania were recruited. Patients had previously failed to respond to at least 6 weeks of the mean equivalent of 500 mg of chlorpromazine daily or to lithium at serum levels averaging 0.8 mEq/L. They were treated with up to 550 mg (mean dose = 343 mg/day) of clozapine monotherapy daily for 13 weeks, with up to 2 mg/day of lorazepam permitted as an adjunct. Of the 15 subjects who completed the study, 87% were considered very much or much improved. As Table 1 shows, 93% of them had an at least 50% improvement on the YMRS. The studies conducted in Cleveland, Ohio, and at McLean Hospital strongly suggest that clozapine is efficacious in the treatment of acute refractory mania. However, randomized controlled trials are needed to confirm these findings.

Table 1. Clozapine in 15 Patients With Hard-to-Treat Mania: Improvement on BPRS, YMRS, and CGI*

Improvement	BPRS	YMRS	CGI
≥ 20%	100%	100%	100%
≥ 50%	86%	93%	71%
≥ 75%	57%	50%	36%

*Zarate CA Jr, Tohen M. 1997. Unpublished data. Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions Scale, YMRS = Young Mania Rating Scale.

Our group conducted a meta-analysis involving primarily retrospective and open-label studies of clozapine available from 1973 through 1995.[4] Patients in manic or psychotic phases of schizoaffective or bipolar disorder were significantly more likely to respond to clozapine than patients with schizophrenia (71.2% of 315 affective patients vs. 61.3% of 692 schizophrenic patients; p = .0006). In addition, in the same review, patients in the manic and mixed-psychotic state of illness were more likely to respond to clozapine than patients with major

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depressive syndromes (72.2% of 79 manic and mixed patients vs. 51.7% of 58 depressed patients; p = .001).

Clozapine in Depression

There are no controlled studies of clozapine in the treatment of the acute or maintenance phase of major depression. However, pooled results of three retrospective studies[92,93,111] indicate that 30 (51.7%) of 58 patients with major depressive syndromes (unipolar, bipolar, or schizoaffective depression) responded to clozapine. Importantly, the majority of these had previously failed to respond to standard treatments.

Clozapine in Mixed Mania

Three retrospective studies examined the efficacy of clozapine in dysphoric mania.[93,112,113] Pooled results of these studies suggest that the incidence of response to clozapine in mixed bipolar states was 69.0% (20 of 29 patients), which were found not to be significantly different from the 30 (51.7%) of 58 patients with major depressive syndromes (unipolar, bipolar, or schizoaffective depression) who responded to clozapine.[5]

Clozapine Monotherapy as a Mood Stabilizer

Four studies[4,110,113,114] suggest that clozapine monotherapy may exert beneficial (i.e., antipsychotic and mood-stabilizing) effects on patients with bipolar and schizoaffective disorder, who were considered either refractory or intolerant to standard therapies including lithium, carbamazepine, valproate, and neuroleptics. In the first study,[113] seven patients with dysphoric mania were treated with clozapine (including three patients who were given clozapine alone); all seven continued to do well over a mean of 4 years of follow-up. The second study[4] found that 11 (65%) of 17 patients with bipolar or schizoaffective disorder were successfully maintained on clozapine monotherapy for a mean of 16 months with no major affective episodes or rehospitalizations. Also, this study suggests that clozapine was helpful in reducing rehospitalizations: the mean ± SD hospitalization rate per 6 months at follow-up during clozapine therapy was 0.4 ± 1.2, significantly lower than before starting clozapine therapy (0.8 ± 1.2, p = .025). The third, an open-label study,[110] reported that 22 patients (11 bipolar and 11 schizoaffective) continued to take clozapine for an average of 15 months (range, 4–46), of whom 31.8% required increase in the dose of clozapine, 22.7% required hospitalization, and 45.5% required the addition of an antidepressant because of major depressive episodes. In the last study, a randomized, open naturalistic trial of clozapine for refractory bipolar patients, Suppes and colleagues (1996)[114] reported a significant improvement in psychotic and manic symptoms by 6 months of treatment that was sustained over the next 6 months; this study confirmed previous findings of clozapine's mood-stabilizing properties.[4]

Predictors of Response to Clozapine

Another study conducted by our group searched for predictors of response to clozapine in patients with affective disorders.[93] In this study, the polarity of the episode appeared to predict response in long-term follow-up. Patients started on clozapine therapy during the manic phase of either bipolar or schizoaffective disorder were more likely to have a favorable long-term outcome compared with patients started on clozapine during the depressed phase of their illness (unipolar, bipolar, or schizoaffective depressed); 72.0% of 67 patients versus 46.7% of 50 patients, p = .008). In addition, the number of previous episodes appeared to predict continued clozapine treatment at follow-up. One or more depressive episodes predicted discontinuation of clozapine (p = .01). In contrast, having had more than one nonaffective psychosis predicted continued clozapine therapy (p = .05). Furthermore, the polarity of the episode at which clozapine was started predicted discontinuation of clozapine. Bipolar manic and schizoaffective bipolar patients were significantly more likely to remain on clozapine therapy as compared with unipolar, bipolar, and schizoaffective depressed patients (p = .001).

ANTIPSYCHOTIC DRUGS AND THEIR ROLE ON FUNCTIONING IN PATIENTS WITH AFFECTIVE DISORDERS

Until recently, it was believed that bipolar patients would generally have a favorable functional outcome after symptomatic control was achieved.[115,116] However, recent long-term studies of bipolar disorder patients suggest that favorable outcomes in terms of functioning are not always achieved after hospitalization.[117–119] The long-term use of neuroleptics in bipolar patients has been reported to be associated with long-term impaired functioning. In a 4-year prospective follow-up of 75 patients hospitalized with mania,[64] our group found that the use of neuroleptic drugs was associated significantly with poor residential status at 6 and 48 months, and poor occupational status at 48 months. Work by Meltzer[120] suggests that clozapine treatment can lead to an improvement in "quality of life" in chronically ill schizophrenic patients. It is thus reasonable to assume that such improvements may extend to affectively ill patients as well. While schizophrenic patients remaining on neuroleptic drugs have been found to worsen in functioning at follow-up, recently, clozapine has been found in two studies to improve functioning in patients with affective disorders refractory to standard therapies. In the first study, Banov and colleagues[93] reported that the social functioning in 47 bipolar and 69 schizoaffective disorder patients treated with clozapine as determined by a series of functional outcome scales (Global Assessment Scale [GAS],[121] Modified Location Code Index,[117] Modified Vocation Status Index[117]) was significantly improved at a mean of 16-month follow-up compared with before starting cloza-

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pine treatment. In the second study,[122] clozapine was found to be effective in improving functioning as determined by the GAS in schizoaffective (N = 25) and bipolar (N = 16) disorder patients followed for a mean of 6 months. The role of risperidone on long-term functioning in bipolar patients has yet to be determined.

NEW ANTIPSYCHOTICS IN LATER-STATE DEVELOPMENT WITH A POTENTIAL ROLE IN BIPOLAR AND SCHIZOAFFECTIVE DISORDER

The mixed dopamine-serotonin antagonist olanzapine was recently released and sertindole is likely to soon be released.[123] Preliminary reports suggest that these drugs may be effective in stabilizing mood or in the management of affective symptoms.

Olanzapine

Olanzapine, a thienobenzodiazepine, is an atypical antipsychotic with high affinity for D_1, D_2, D_3, D_4, 5-HT_2, 5-HT_3, 5-HT_6, α_1-adrenergic, muscarinic M_1, and histaminic H_1 receptors.[124] Olanzapine, in double-blind clinical trials, has at intermediate (7.5–12.5 mg/day) and high (12.5–17.5 mg/day) dosages been found to be superior to placebo and equivalent to haloperidol in the treatment of positive symptoms and superior to both placebo and haloperidol in the treatment of negative symptoms.[124–126] Two studies suggest that olanzapine may have a role in the treatment of affective symptoms. In the first study,[126] patients treated with 10 mg/day of olanzapine were noted to have a significant reduction in scores on the Hamilton Rating Scale for Depression in comparison to those treated with 1 mg/day or placebo. In a subanalysis of a larger database,[124] olanzapine, in a 6-week, double-blind study of schizoaffective disorder bipolar manic patients, had a mean 6.06 decrease in the BPRS mania score compared with a 3.36 mean decrease for the haloperidol group ($p = .251$). Schizoaffective depressed type patients had a 3.59 mean decrease with olanzapine and a 0.33 mean decrease with haloperidol ($p < .0001$).[127]

Sertindole

Sertindole is an atypical antipsychotic with high affinity for 5-HT_2, D_2, and α_1-adrenoreceptors; slightly lower affinity for D_1 receptors, α_2-adrenergic, histaminic H_1, and muscarinic M_1 receptors.[123] Sertindole in double-blind placebo-controlled studies in schizophrenic patients has been shown at a daily dose of 12–24 mg/day to be superior to placebo and comparable with haloperidol (4–16 mg/day) in reducing positive symptoms. Daily doses of 20–24 mg/day proved effective against negative symptoms of schizophrenia.[128,129] Recently, in an open-label safety study of sertindole in 20 patients with a diagnosis of schizoaffective disorder, patients were maintained on sertindole (mean dose = 24 mg/day) and divalproex sodium (mean dose = 1000 mg/day) for up to 11 months. Sertindole was reportedly effective in stabilizing mood and was well tolerated when combined with divalproex.[130]

Furthermore, both olanzapine and sertindole have been reported to have a low incidence of extrapyramidal symptoms.[124,128–130] If these drugs in further testing continue to show benefit in alleviating mood symptoms and mood stabilizing properties and have a low risk for extrapyramidal side effects, then they could possibly become a significant contribution to the armamentarium in the treatment of bipolar disorder.

CONCLUSION

This review discussed the role of antipsychotics throughout the past 40 years in the treatment of bipolar manic-depressive illness. Prior to the introduction of lithium, neuroleptics were the primary somatic therapies for bipolar disorder. Their role later became secondary in the management of bipolar disorder after the introduction of mood stabilizers (lithium, carbamazepine, and valproate), as the use of neuroleptics was discouraged because of their side effect profile. In spite of the significant adverse effect profile of the standard antipsychotic medications, a substantial number of bipolar patients are exposed to neuroleptics. In part, this may be explained by the fact that a significant number of patients still fail to respond to conventional therapies.

The atypical antipsychotic agents already released (clozapine, olanzapine, and risperidone) and being tested (sertindole) appear to show promise as alternative therapies for patients with schizoaffective and bipolar disorder. Controlled studies are needed to determine the exact nature and extent of each agent as an antimanic, antidepressive, antipsychotic, and mood-stabilizing agent. Furthermore, their side effect profile as well as potential drug interactions with conventional drugs used in the treatment of bipolar disorder will need to be further evaluated.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin), clozapine (Clozaril), divalproex sodium (Depakote), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigene (Lamictal), lorazepam (Ativan and others), olanzapine (Zyprexa), pimozide (Orap), sertindole (Serlect), risperidone (Risperdal), thiothixene (Navane).

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