ABSTRACT

Schizophrenia and bipolar disorder are distinguished primarily by course of illness and, consequently, share many similar symptoms cross-sectionally. This similarity presents a diagnostic challenge for clinicians, because accurate diagnosis often requires monitoring patients over time; however, treatment typically needs to be instituted quickly, further complicating this process. Conventional antipsychotics have been used to treat both conditions, but have proved to have little utility in the long-term management of bipolar disorder, and considerable side-effect liability for the long-term management of schizophrenia. The newer, second-generation antipsychotics have improved tolerability relative to the older agents and may provide thymoleptic properties, including affective relapse prevention, that expands our treatment armamentarium for new-onset psychotic and affective disorders.

Michael our current conceptual understanding of schizophrenia is based on observations made by the German psychiatrist Emil Kraepelin, who in 1896 described a group of psychotic patients who developed impaired cognition in their 20s or 30s, typically ending in poor outcome. Kraepelin proposed the separation of this syndrome, dementia praecox, from manic-depressive insanity, which shared many common features, primarily based on differences in the course of illness. Whereas he characterized dementia praecox (later reconceptualized and renamed schizophrenia) as a chronic, deteriorative disease, manic-depressive insanity (later renamed and reconceptualized as bipolar disorder) featured an episodic course and more favorable outcomes. Despite Kraepelin's historic definition of and differentiation between 2 distinct psychotic disorders, considerable overlap between them persists more than 100 years later.

The psychopathology of schizophrenia is usually described in terms of 3 somewhat independent symptom clusters: positive, negative, and disorganized. Positive symptoms include psychotic symptoms, such as delusions and hallucinations. Negative symptoms include withdrawal, impoverished emotional state, motivational difficulties, lack of energy, affective flattening, loss of spontaneity, and lack of initiative. Disorganization as a syndrome of schizophrenia includes incoherence, illogicality, loose associations, inappropriate affect, and poverty of thought content. Many of these symptoms also occur in bipolar disorder.

Depression and anxiety are commonly associated with bipolar disorder, and are also common in schizo-

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phrenia. Bipolar disorder (particularly in the manic phase) and schizophrenia can be quite indistinguishable. For example, psychosis, which is used as one of the major diagnostic criteria in schizophrenia, is also common in bipolar disorder, affecting up to 80% of manic patients. Similarly, depression, which is a major feature of bipolar disorder, affects up to 80% of people with schizophrenia, even at the first episode. Likewise, neither manic nor neurovegetative symptoms are definitive in the differential diagnosis between these conditions. Also, although it is not widely recognized, depressed patients with bipolar disease display a broad pattern of cognitive impairments that are somewhat similar to those seen in schizophrenia. Cognitive impairment, which is most evident during acute affective bipolar episodes, persists throughout the course of the disorder, although to a lesser degree than in schizophrenia. Finally, the negative symptoms that characterize schizophrenia very much resemble depression, particularly during acute phases (Table 1).

One way psychiatry has attempted to fill the gap between these distinct psychoses is by defining another disorder that bridges them. When mood symptoms are a major feature of a patient with otherwise characteristic schizophrenia, the diagnosis of schizoaffective disorder is made. Thus, schizoaffective disorder may be viewed as a mild schizophrenia, a severe bipolar disorder, or even a combination or continuum of both disorders.

Making the differential diagnosis between schizophrenia and bipolar disorder is most problematic in patients presenting with a first episode of psychosis, at that point, the longitudinal course of illness— which best distinguishes these disorders— is not clinically observable. Rather, the patient and family are typically confused about what is taking place. Because long-term information is not yet available, the psychiatrist must make a preliminary diagnosis based on the relative prominence of mania or depression compared with psychotic and cognitive symptoms. Because none of these symptoms is diagnostically specific, making a diagnosis can be difficult. Family history of either schizophrenia or bipolar disease, of course, may inform this diagnosis; however, these data also are not diagnostically specific.

The final diagnosis, therefore, will not be truly defined until the patient is observed during the course of months, and sometimes years. Some early medical evidence has shown that the time between a first and second manic episode can be as long as 3 years. Treatment response will also help to further define the diagnosis.

Even with the benefit of time and continuing clinical observation, diagnoses may be quite variable. Fennig et al analyzed diagnoses for patients with first-episode psychosis and found that, even with careful assessments based on structured interviews and expert opinion, up to 14% of even broad-based diagnoses were changed. More specific diagnoses, such as subtypes of schizophrenia or affective illness (eg, bipolar disorder, paranoid schizophrenia), were changed in 14% to 30% of patients. Forty-three percent of the changes in diagnosis were attributed to the clinical course of the illness; the rest were attributed to the diagnostic process itself.

We conducted a study that observed patients who clearly met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for mania at the first episode. Over the course of 1 year, we found that 12% of those patients progressed to schizoaffective or schizophrenic disorders. Thus, the manic syndrome, predictive 88% of the time, failed 12% of the time. Finally, our 1994 review of the diagnosis of schizophreniform disorder, which typically is defined clinically as “early schizophrenia,” showed that only 60% of patients diagnosed with schizophreniform disorder actually progressed to schizophrenia. An additional 30% developed affective disorder, and only 10% maintained the initial diagnosis of schizophreniform disorder—a relatively brief, remitting nonaffective psychosis.

Because therapies can sometimes be differentially effective in treating various symptoms and components of schizophrenia and bipolar disorder, it is important to

<table>
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<tr>
<th>Symptoms</th>
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<th>Bipolar Disorder</th>
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<tr>
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<td>Negative†</td>
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* Manic syndrome relatively specific for bipolar disorder.
† Negative syndrome relatively specific for schizophrenia.
No defining symptoms for either condition.

Table 1. Schizophrenia and Bipolar Disorder: Common Symptoms
understand the diagnostic similarities and boundaries between the disorders to optimize treatment.

**Antipsychotics and Mood Stabilizers in Bipolar Disorder**

By definition, mood stabilizers ameliorate affective and psychotic symptoms during acute manic episodes, improve depressive symptoms during acute bipolar depressive episodes, and prevent additional mood episodes. Lithium has been the primary treatment for bipolar disorder for more than 50 years, but new medications with potential mood-stabilizing effects are providing more options. Divalproex and olanzapine have gained approval by the US Food and Drug Administration (FDA) for the treatment of manic episodes, and data from placebo-controlled trials in patients with acute mania suggest that both drugs are also effective in treating psychotic symptoms and improving cognitive function. Emerging clinical data for the new atypical antipsychotics support the use of several of these compounds in mania as well as in depression, and the prevention of future affective episodes (Table 2).

The introduction of the drug aripiprazole, the newest antipsychotic agent approved for the treatment of schizophrenia, adds to the therapeutic armamentarium for mania as well. Randomized controlled studies of aripiprazole in mania demonstrated a similar efficacy to olanzapine (Figure 1). In a new unpublished study, a 3-week double-blind trial of aripiprazole 30 mg daily versus placebo in 272 hospitalized patients with acute mania, aripiprazole demonstrated significant improvement in symptoms of acute mania as measured by the Young Mania Rating Scale (YMRS). Significant improvements were seen from day 4 and were maintained throughout the study. In addition, the response rate was significantly higher in the aripiprazole group compared with the placebo group (51% vs 31%, \( P < .001 \)). The overall discontinuation rate due to adverse events was similar between the aripiprazole and placebo groups. Furthermore, there were no significant changes in body weight in patients taking aripiprazole compared with placebo.

Similar findings have been reported with risperidone and quetiapine; the FDA is now reviewing applications for all 3 of these compounds for use in bipolar disorder. Consequently, we may soon see several new approved treatments available for use in acute mania.
Another advance in the treatment of bipolar disorder is the use of atypical antipsychotics in combination with classic mood stabilizers to achieve greater efficacy. As little as 5 years ago, available medical evidence suggested that lithium or divalproex could (and perhaps should) be used as monotherapy in the treatment of acute mania. No data existed to support increased efficacy for the addition of an antipsychotic agent to this regimen, although such adjunctive therapy was used frequently in clinical practice.

Recent clinical trial reports now support the validity of this clinical practice. The first was a double-blind controlled study of 156 patients with bipolar disorder who were randomized to receive lithium or divalproex combined with placebo, risperidone (mean dose, 3.8 mg daily) or haloperidol (mean dose, 6.2 mg daily).15 The combination of an antipsychotic plus lithium or divalproex was more efficacious than mood-stabilizer monotherapy by the end of the first week. This improvement in efficacy with combination therapy was evident in patients with and without psychotic features (Figure 2). However, by week 3, the mood stabilizer began to demonstrate signs of improving efficacy, supporting the early lithium data reporting its efficacy as both an effective antimanic and antipsychotic in patients with bipolar disorder.

A study of olanzapine as adjunct therapy was designed somewhat differently; 344 patients with bipolar disorder initially were given divalproex or lithium.16 Nonresponders were then also given olanzapine (5–20 mg daily) or placebo as adjunct therapy. Olanzapine therapy improved patients' YMRS total scores significantly more compared with mood-stabilizer monotherapy, showing superior efficacy in the treatment of manic and mixed bipolar episodes (Figure 3). Adjunct treatment was effective in patients with or without psychoses, a finding that speaks to the widespread clinical assumption that antipsychotics treat psychosis only and that a mood stabilizer must be added to treat the mood disorder. This thinking may be flawed—to a large extent, the psychosis of mania may be just another severity measure of mania, a marker of the severity of this condition. Therefore, effectively treating the manic symptoms may effectively treat the psychotic symptoms in bipolar patients as well. As suggested by this study, atypical antipsychotics are not simply effective for treating the psychotic fea-
tures of mania, but also for treating mania overall, independent of psychosis. Because nonpsychotic mania is slightly less severe, Figure 3 shows a slightly better response to adjunctive therapy in that treatment group.

In a third study, the first double-blind controlled study to be conducted in adolescent mania, 30 adolescents with manic or mixed bipolar disorder received an initial dose of divalproex (20 mg/kg) and were randomly assigned to 6 weeks of combination therapy with quetiapine titrated to 450 mg daily or placebo. Two significant findings were reported: divalproex alone was effective, and a significant number of patients achieved better results with combination therapy. More patients achieved the predefined point of remission (YMRS score of 12) on combination therapy compared with patients taking divalproex alone. The YMRS response was more rapid and significantly greater with combination therapy (87% vs 53% taking placebo; Fisher exact test, \( P = .05 \)).

Similar, but in some ways converse, results have been reported in patients with schizophrenia. Casey and colleagues investigated the use of divalproex as adjunctive therapy to an antipsychotic agent in 249 hospitalized patients who were randomized to receive olanzapine monotherapy, risperidone monotherapy, divalproex plus olanzapine, or divalproex plus risperidone for 28 days. The combination therapy group was significantly better than the monotherapy group at days 3, 5, 7, 10, 14, and 21, but not at day 28. A statistically significant treatment difference between the combination therapy group and monotherapy group over the 28 days of the study \( (P = .020) \) was obtained in a post-hoc repeated measures analysis of variance.

The results of this study prompt some interesting questions as to which therapies act as mood stabilizers and which therapies are useful for schizophrenia (ie, as antipsychotics). Although further investigation is clearly warranted, these results suggest that our current therapeutic tool box, with drugs indicated for specific use as antipsychotics or mood stabilizers, actually treat a host of symptoms shared by both bipolar and schizophrenic patients. Judicious use of these medications in combination therapy may achieve better results than monotherapy, but runs the risk of added side effects.

Although the combination therapies described here are, for the most part, pharmacokinetically harmonious, pharmacodynamic interactions are more problematic. For example, 2 drugs that cause weight gain or sedation used in combination will increase the risk of either side effect. The same is true for drugs with cardiac and metabolic side effects. The quandary for clinicians is to weigh the increased risk of side effects in combination therapy against its therapeutic advantages in individual patients. This approach is in keeping with Meyer's historic concept of psychiatric practice as residing within individualization of treatment and patient management. Table 3 serves as a resource for making these clinical decisions and incorporates findings relating to the newest antipsychotic aripiprazole.

For long-term use, typical antipsychotics, such as haloperidol and chlorpromazine, have proven efficacy in mania but become less tolerable over time. A Scandinavian study of the drug flupentixol decanoate, a conventional antipsychotic similar to haloperidol, showed that when the drug was given to bipolar patients with symptoms of both mania and depression, the patients experienced a decrease in mania, but a corresponding increase in depressive symptoms. This study illustrates the risk that most psychiatrists must consider when treating bipolar patients with conventional antipsychotics—namely, not managing, or potentially precipitating, depression.

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<th>EPS</th>
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++++ = side effect is very common or severe; +++ = side effect is common or moderately severe; ++ = side effect is moderately common or of mild severity; + = side effect is relatively uncommon or is mild; 0 = side effect does not occur or is entirely benign.

CNS = central nervous system; EPS = extrapyramidal symptoms; GI = gastrointestinal.

Data from Strakowski et al.
LONG-TERM PROFILE OF ATYPICAL ANTIPSYCHOTICS

Will the long-term risk profile improve with the new atypical antipsychotics? Data from a relatively long-term trial (12-week) of haloperidol vs aripiprazole reported significantly fewer side effects for aripiprazole.21 Figure 4 demonstrates the time to discontinuation for all reasons, including adverse events and lack of efficacy. In another recent study comparing olanzapine to lithium in the management of bipolar disorder over the course of 13 months, patients taking olanzapine were more likely to remain in the study and to maintain remission.22

CONCLUSION

As Kraepelin noted more than a century ago, schizophrenia and bipolar disorder share many symptoms, and clinicians are left with the dilemma of distinguishing between the disorders. Ultimately, the diagnosis is made over the course of the illness, but the need for treatment is immediate. Recent studies suggest that at least some of the atypical antipsychotics may provide long-term mood-stabilizing properties. Continuing research will demonstrate the efficacy of these agents as maintenance therapy. Although additional investigation is warranted, these initial findings further blur the boundaries between bipolar disorder and schizophrenia and suggest that some treatments are effective across all phases of both disorders. Although the boundaries between the disorders are sometimes transparent, diagnosis is nonetheless an important clinical process.

Eventually, the nonspecific treatments currently available will be replaced by more targeted therapies. It is important to remember that acute treatments are not necessarily the same as maintenance therapies. Whereas combination therapies have been shown to be effective in acute mania, combination therapy need not be maintained indefinitely. It is in the best interest of patients to minimize drug treatment as much as possible; clinicians should strive to achieve monotherapy over the course of the illness.

REFERENCES


