Management of Acute Mania

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Bipolar disorder is a lifelong episodic condition characterized by mood swings between mania and depression. In the United States alone, approximately 4 million people are affected by this disorder. Pharmacologic treatment for acute manic episodes or as maintenance therapy includes lithium, valproate, carbamazepine, and typical antipsychotics. However, many patients fail to respond to these treatments due to lack of efficacy or production of side effects leading to patient noncompliance. Noncompliance with pharmacologic treatment is indeed a major risk factor in bipolar disorder patients and needs to be managed with ongoing education, psychotherapy, and a simplified but effective pharmacologic treatment regimen. Recently introduced novel antipsychotics show much promise as mood-stabilizing agents in bipolar patients, with minimal risk of treatment-emergent extrapyramidal symptoms and tardive dyskinesia. Nonetheless, further research is warranted to help clarify the role of novel antipsychotics in the treatment of bipolar disorder.

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Bipolar disorder is a highly prevalent condition that causes a great deal of human suffering. First systematically described in the scientific literature in 1921,[1] bipolar disorder has an episodic nature, characterized by manic or depressive episodes followed by symptom-free periods.

EPIDEMIOLOGY

The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) Project estimates the lifetime prevalence of bipolar disorder to be 0.8%.[2] The 1-month point prevalence (the proportion of individuals ill at any single point in time) for bipolar disorder has been estimated as 0.4%, which in 1996 would translate to approximately 1 million Americans. The National Comorbidity Survey (NCS) estimates the lifetime prevalence for bipolar disorder at 1.6%[3]; hence, 4 million Americans will suffer from bipolar disorder at some point in their life. Studies from countries outside the United States report similar rates.[4]

Incidence rates, or the number of newly diagnosed cases of bipolar disorder during a defined period of time, are difficult to estimate. However, in recent years an increasing number of patients have been hospitalized with affective disorders.[5] This increase might be explained by changes in diagnostic criteria. Another explanation is treatment-orientated diagnostic bias, which occurs when clinicians preferentially diagnose one condition over another when new pharmacologic treatments become available.[5]

RISK FACTORS

Evidence of genetic risk factors in bipolar disorder is well documented.[6] Molecular genetics has made great strides in recent years, with at least 2 groups providing evidence suggesting that chromosome 18 carries the genetic risk for bipolar disorder.

Two controversial risk factors for bipolar disorder are socioeconomic class and gender. In one population-based study,[7] bipolar disorder appears overrepresented in the higher socioeconomic classes. This finding is replicated in neither the ECA nor the NCS studies, however. Similarly, most researchers report no gender differences with respect to bipolar disorder, although some studies show conflicting data in regard to gender prevalence.[6]

Stressful life events or trigger events (e.g., the death of a loved one) are considered contributing factors of bipolar disorder relapse early in the course of the illness. A cause-and-effect association between these trigger events and relapse in patients who have experienced fewer than 2 or 3 episodes is shown in a number of studies. This correlation has not been found in multiple-episode patients,[6] as relapse in these patients is typically spontaneous. Hence, a clear cause-and-effect association between stressful events and relapse no longer exists.

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COURSE AND OUTCOME

Bipolar disorder is a lifelong episodic condition with multiple episodes of mania or depression occurring in over 90% of patients.[8] In many cases, repeated episodes will lead to a downhill course with progressively deteriorating levels of functioning and poor treatment response.[6] Furthermore, as the frequency of episodes increases, the severity of residual symptoms between episodes increases. Certain types of symptoms, specifically, mixed symptoms[9] and substance abuse,[9] are recognized as predictors of increased episode length.

There are a number of predictors of relapse. An increased number of previous episodes increases the risk of further relapses.[6] Specific symptoms predicting relapse include psychotic features, especially mood-incongruent psychotic features,[10] and depressive symptoms.[11] Comorbid conditions, specifically alcoholism and interepisode subsyndromal symptoms, are also predictors of relapse.[6]

PSYCHIATRIC MANAGEMENT

The American Psychiatric Association (APA) recently published practice guidelines addressing psychosocial and somatic interventions for the treatment of bipolar disorder.[12] Among psychosocial interventions, emphasis is placed on the establishment and maintenance of a therapeutic alliance between the patient and a clinician who can provide a long-term supportive relationship. This relationship should be established within the framework of a partnership allowing the identification of significant trigger events or stressors, as well as interepisode subsyndromal symptoms that may affect the course of the illness. An important aspect of the therapeutic alliance is the clinician's role in providing education, not only to the patient but also to the family.[13,14]

PHARMACOLOGIC TREATMENT

In the early 1970s, the U.S. Food and Drug Administration (FDA) approved lithium carbonate for the treatment of mania. The efficacy of lithium in acute and maintenance treatment of bipolar disorder has been clearly documented.[8] Although the risk of serious adverse effects (e.g., renal failure) is low, mild adverse effects (e.g., polydipsia and polyuria) with lithium appear to be quite common.[15] Neurocognitive impairment represents the most frequent reason for patient noncompliance with lithium.[8] Approximately 20% to 40% of patients with acute mania fail to respond to lithium.[16]

The FDA recently approved divalproex for the treatment of acute mania.[17,18] A double-blind, placebo-controlled trial[17] included patients with poor response or lack of tolerability to lithium. The results demonstrated a superiority of divalproex over placebo for the treatment of acute mania. Another study included a 3-arm design comparing divalproex, lithium, and placebo.[18] Both active treatments were statistically significantly superior to placebo with no difference noted between the two. Regarding patient satisfaction, 11% of patients discontinued lithium due to adverse effects compared with only 6% of those taking divalproex. At least one study[19] has suggested that divalproex has a faster onset of action compared with lithium (10–14 days).[15]

Valproate is also used as maintenance treatment for bipolar disorder. A study conducted in Europe compared valpromide (an amide derivative of valproate) with lithium in the treatment of bipolar disorder and showed no difference in terms of efficacy.[20] Of 150 patients, 42 taking lithium relapsed compared with 39 taking valpromide. The study design allowed patients to switch from one treatment to the other in case of poor response or lack of tolerability. Four patients switched from valpromide to lithium and 10 from lithium to valpromide. Six of the 10 patients switching from lithium to valpromide did so due to lithium-induced adverse effects.

Predictors of poor response to lithium include mixed symptoms,[2] a history of multiple episodes, and comorbid substance use disorders.[15] In contrast, patients with multiple episodes and comorbid substance use disorders have demonstrated a good response to divalproex.[15,18]

Other treatments currently not approved for bipolar disorder by the FDA have been used for the treatment of mania, including carbamazepine, typical and novel antipsychotics, lamotrigine, and gabapentin. While efficacy for the acute treatment of mania using carbamazepine is well documented,[15] maintenance studies show mixed results.[21–23] Due to its adverse effect profile, carbamazepine has low patient acceptability.[24,25] The most common adverse effects include blood dyscrasia, headache, nausea, and skin rash.[15,26] Also, due to its self-inducing metabolism, blood levels of carbamazepine need to be closely monitored. Additionally, carbamazepine has many drug interactions with other mood stabilizers and several other types of medications.

Typical antipsychotic agents are often used during acute treatment of manic symptoms. They do not have a large role in maintenance therapy, though, because of side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia. Furthermore, typical antipsychotics do not show adequate efficacy in the treatment or prevention of depressive symptoms.[27] The novel antipsychotic clozapine has demonstrated mood-stabilizing properties in treatment-resistant bipolar disorder,[28] but its use is limited by the risk of agranulocytosis. Risperidone, another novel antipsychotic, has also been used to treat bipolar disorder. Initial reports suggest that risperidone, when combined with mood-stabilizing agents, exhibits mood-stabilizing or antimanic activity.[27,29] Olanzapine, another novel antipsychotic, shows promise as a mood stabilizer in the treat-

ment of bipolar patients.[30] Preliminary results of a large double-blind trial showed olanzapine to be statistically significantly superior compared with placebo in mean reductions of the Young Mania Rating Scale (YMRS) (–10.3 vs. –4.9, p = .019) and the Positive and Negative Syndrome Scale (PANSS) total score (–11.1 vs. –3.1, p = .019) and PANSS positive score (–4.7 vs. –2.0, p = .040) from baseline to endpoint.[31] Clinical response in this trial was defined a priori as a reduction of ≥ 50% in YMRS from baseline to last measurement in acute treatment. When this definition was used, there was a statistically significantly greater number of responders taking olanzapine than those taking a placebo (48.6% vs. 24.2%, p = .004). Furthermore, olanzapine demonstrated a favorable profile versus conventional antipsychotics in trials of schizophrenic and schizoaffective patients, with respect to minimizing the risk of EPS[32] and tardive dyskinesia.[33] Similarly, olanzapine demonstrated a favorable profile in schizophrenia and schizoaffective patients versus risperidone, with respect to minimizing treatment-emergent EPS as assessed by 3 rating scales in a large, double-blind trial.[34] These results appear very promising. However, further studies and clinical experience will help to clarify the role olanzapine will play in the treatment of bipolar disorder.

Figure 1 presents a suggested algorithm for the treatment of acute mania. A number of drugs including anticonvulsants, antipsychotics, calcium channel blockers, thyroid replacement hormones, and choline are currently used in refractory bipolar patients.

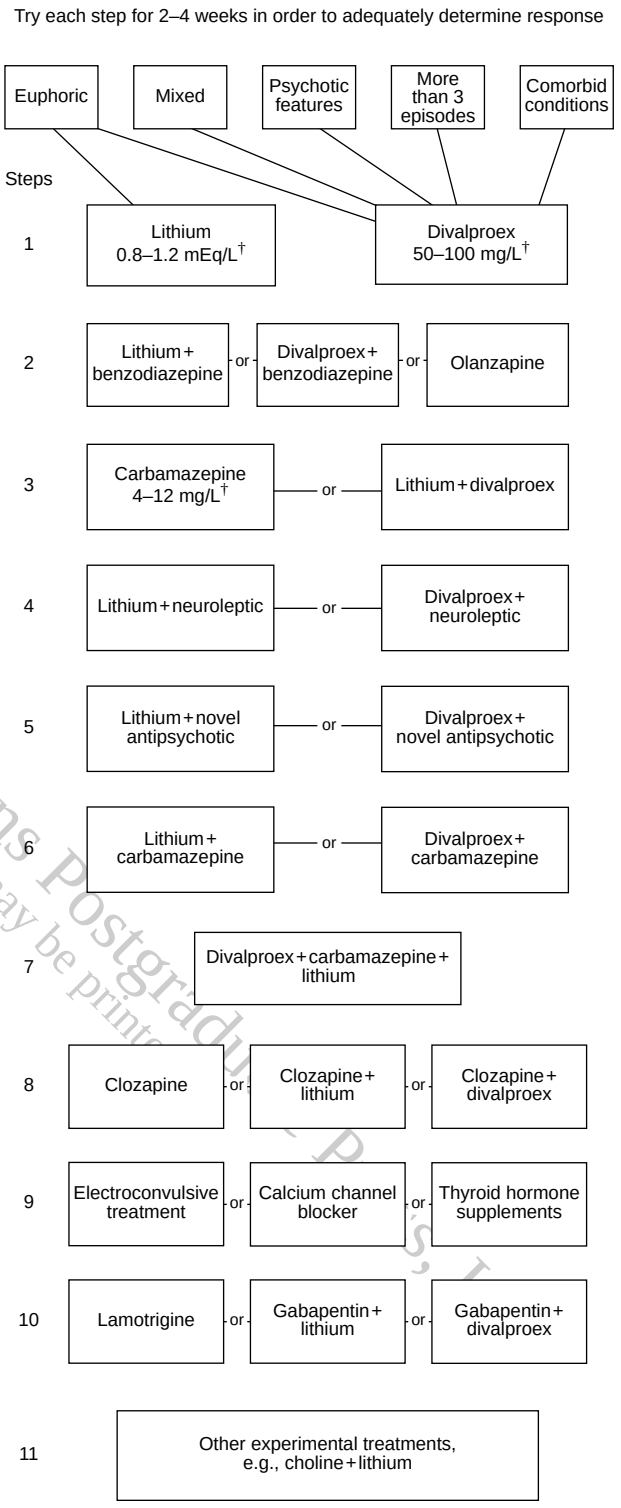
NONCOMPLIANCE

Noncompliance with pharmacologic treatment has been identified as a major risk factor in bipolar disorder.[8] For example, noncompliance with mood stabilizers is estimated to be close to 50%.[35] A recent report documented a 57% noncompliance rate in first-episode bipolar patients and a 27% noncompliance rate in multiple-episode patients.[36] To some extent, it is not surprising that a large proportion of individuals suffering from bipolar disorder are noncompliant. The risk of noncompliance increases in episodic conditions where the short-term disadvantages of adverse effects appear to outweigh, in the perception of the patient, the long-term benefits of relapse prevention provided by long-term pharmacologic treatment. Additionally, many noncompliant patients perceive a benefit from hypomania concerning creativity and feelings of attractiveness.[8] The presence of substance use disorder with bipolar disorder has also been identified as a risk factor of noncompliance with pharmacologic treatment.[8,10]

MANAGEMENT OF NONCOMPLIANCE

Ongoing education about bipolar disorder in combination with psychotherapy is important to prevent noncom-

Figure 1. Pharmacologic Treatment of Acute Mania[a]



[a]If at any step there is adequate response, maintain on current treatment. If there is no response, partial response, or adverse effects, proceed to the next step. As of September 1998, only lithium and divalproex have been approved by the FDA to treat mania. Novel antipsychotics for this table include: risperidone, sertindole, and quetiapine.
†Desired blood drug levels.

pliance. Short- and long-term education in an individual or group setting can improve compliance to pharmacologic treatment.[37,38]

A relatively straightforward method for management of noncompliance is the simplification of pharmacologic treatment. For example, in lifelong conditions where patients self-administer medication, 4 times daily dosing leads to a 57% noncompliance rate compared with only 27% noncompliance rate for once-daily dosing.[39]

CONCLUSIONS

Currently, approximately 1 million Americans suffer from bipolar disorder. This disorder can be incapacitating for its sufferers. Therapy has improved over the past 45 years, with the addition of chlorpromazine in the 1950s, lithium in the 1970s, and divalproex in the early 1990s. However, many patients are still unable to get adequate relief. With the recent advent of novel antipsychotics, especially olanzapine, patients with bipolar disorder may be better able to control their symptoms. Further research is warranted to determine where and when the novel antipsychotics should be used in the treatment of bipolar disorder.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), divalproex (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

The following agent mentioned in this article is *not* indicated for the treatment of bipolar disorder: olanzapine.