Clinical Decision Making in the Treatment of Mania

Roy H. Perlis, M.D., M.Sc.

Nine agents are now Food and Drug Administration–approved for acute treatment of bipolar mania, and several other agents are being studied for efficacy. With multiple treatment options available, clinicians face the challenge of selecting among agents. Although clinicians may consult the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Bipolar Disorder*, Second Edition, when selecting a treatment for bipolar mania, decisions about many aspects of treatment, such as choosing among agents, comparing combination therapy versus monotherapy, and individualizing treatments, remain complex. Considering data from recent clinical studies that have compared the efficacy, safety, and tolerability of medications for bipolar mania both between and within classes may facilitate such treatment decisions. *(J Clin Psychiatry 2008;69[suppl 5]:16–21)*

Bipolar disorder is typically characterized by both manic/hypomanic and depressive episodes, often with periods of normal mood or euthymia between episodes. During manic episodes, individuals may become restless, irritable, easily distracted, and impulsive, often demonstrating poor judgment. This behavior may have serious consequences in terms of social and occupational functioning.[1,2] Fortunately, pharmacologic options for the treatment of bipolar mania continue to broaden; 9 agents are now approved by the U.S. Food and Drug Administration (FDA) for the treatment of mania, with further studies ongoing. However, with multiple treatment options available, clinicians may have difficulty selecting from among these agents. An analysis of the efficacy, safety, and tolerability of agents being used to treat mania may help clinicians make effective decisions.

GUIDELINES FOR THE PHARMACOLOGIC MANAGEMENT OF BIPOLAR MANIA

To encourage evidence-based treatment decisions in clinical practice, the American Psychiatric Association (APA) and other organizations publish practice guidelines. Guidelines are based on a comprehensive literature review, with a focus on systematic reviews and randomized con-

trolled trials, as well as expert consensus.[3,4] Clinicians should view guidelines as a starting point for making treatment decisions; they are not absolute and may be altered to suit individual patients and to incorporate clinicians' own judgment.[5] However, when evidence exists, it is important to incorporate it into clinical decision making, as treatments that may "seem" effective can fail to demonstrate efficacy when subject to rigorous study.

APA Practice Guideline Recommendations for Treating Manic or Mixed Episodes

Summary of guidelines. According to the APA practice guidelines,[6] the first-line recommendation for treatment of severely ill patients with manic or mixed episodes is lithium or valproate plus an antipsychotic, preferably an atypical antipsychotic. For first-line treatment of less ill patients, the recommendation is lithium, valproate, or antipsychotic monotherapy. For first-line treatment of a breakthrough episode, the recommendation is to optimize the patient's current medication; if this is not successful, the addition of an antipsychotic is recommended.

Use of guidelines. Because evidence-based treatments are essential to the successful management of patients with mental illness, the use of practice guidelines, such as those of the APA, would seem beneficial in clinical practice. However, a recent study[7] found that guidelines were not consulted by more than one third of clinicians when making treatment decisions. The most common reason given by clinicians for not consulting guidelines was that the recommendations do not address certain features of their patient populations. Thus, practice guidelines need to better address the treatment of patients' symptomatic characteristics and clinical presentations.

Aspects of treatment that guidelines should address. One important consideration not fully addressed in many guidelines is how to choose among the various agents for the treatment of mania. Medications from 3 different
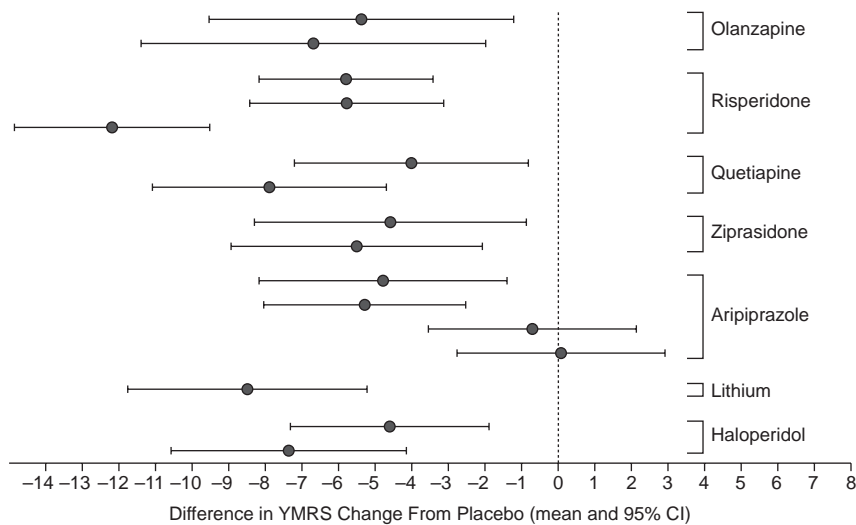
Figure 1. Monotherapy Efficacy of Atypical Antipsychotic and Active Comparators Relative to Placebo in Individual Trials[a]

Olanzapine
Risperidone
Quetiapine
Ziprasidone
Aripiprazole
Lithium
Haloperidol

−14 −13 −12 −11 −10 −9 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2 3 4 5 6 7 8
Difference in YMRS Change From Placebo (mean and 95% CI)

[a]Reprinted with permission from Perlis et al.[8] Bars represent 95% confidence intervals.
Abbreviation: YMRS = Young Mania Rating Scale.

classes are approved to treat mania, including the atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole; the typical antipsychotic chlorpromazine; and the anticonvulsants lithium, divalproex, and carbamazepine.

If medications for mania have similar efficacy, their effectiveness is determined by their safety and tolerability. However, safety and tolerability data are difficult to incorporate into practice guidelines.

EFFICACY OF ATYPICAL ANTIPSYCHOTICS IN ACUTE MANIA

Because clinical trials of treatments for acute mania are abundant as well as similar in design and outcomes measured, reviewing meta-analysis results may provide a fairer comparison than reviewing data from individual studies. Two recent meta-analyses[8,9] provided data that clinicians can incorporate into their decision-making process. Colleagues and I[8] compared the efficacy of FDA-approved atypical antipsychotics in the treatment of acute mania by conducting a meta-analysis of randomized, placebo-controlled monotherapy and combination therapy trials. Change in score on the Young Mania Rating Scale (YMRS) or the Mania Rating Scale (MRS) from baseline to endpoint was used to measure efficacy.

Atypical Antipsychotic Monotherapy Clinical Trials

The monotherapy trials in our meta-analysis[8] included 1881 drug-treated subjects and 1233 placebo-treated subjects. Aripiprazole was tested in 4 trials; risperidone was tested in 3 trials; olanzapine, quetiapine, and ziprasidone

were each tested in 2 trials. An active comparator (lithium or haloperidol) was included in addition to placebo in 3 trials. In the individual trials, all of the agents demonstrated similar efficacy relative to placebo (Figure 1). Pooled results showed no significant differences among the atypical antipsychotics and no pairwise significant differences. Patients achieved a clinical response (defined as 50% reduction in YMRS score from baseline to endpoint) in 8 of 12 trials. Overall rates of response were 53% for active medications and 30% for placebo.

In the pooled monotherapy results reported by Scherk et al.,[9] the atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) were significantly superior to placebo (p < .001) according to changes in YMRS scores. While each agent was individually significantly superior to placebo in symptom change, the response rate for quetiapine versus placebo was not significantly different.

Atypical Antipsychotic Combination Therapy Clinical Trials

The combination therapy trials in our meta-analysis[8] included 673 drug-treated subjects and 517 placebo-treated subjects. In addition to a mood stabilizer, adjunctive risperidone and quetiapine were each tested in 2 trials, olanzapine and ziprasidone were each tested in 1 trial, and no trials of aripiprazole were identified. Haloperidol was used as a comparator in 1 adjunctive therapy trial. In the individual trials, all of the agents demonstrated efficacy in combination therapy relative to placebo (Figure 2). No significant difference among the agents was found, and no pairwise significant differences were found. Notably, however, ziprasidone had a confidence interval centered near zero, although confidence intervals were wide.

Although combination therapy studies reported less improvement on the YMRS than monotherapy trials, with a pooled difference in score of 4.1 (95% CI = 1.7 to 6.6) versus 5.5 (95% CI = 4.0 to 7.1), no conclusions can be made regarding the efficacy of one form of therapy versus another because the results are not directly comparable.[8] Different control groups were used for monotherapy and combination trials (placebo vs. mood stabilizer plus placebo, respectively).

Limitations of these meta-analyses. Perlis et al.[8] noted that, although the pooled studies were similar in design, heterogeneity existed. For example, severity of mania varied slightly among studies; some were international and

Roy H. Perlis

Figure 2. Efficacy of Atypical Antipsychotic and
Active Comparator Relative to Placebo Combined With
Mood Stabilizers in Individual Trials[a]
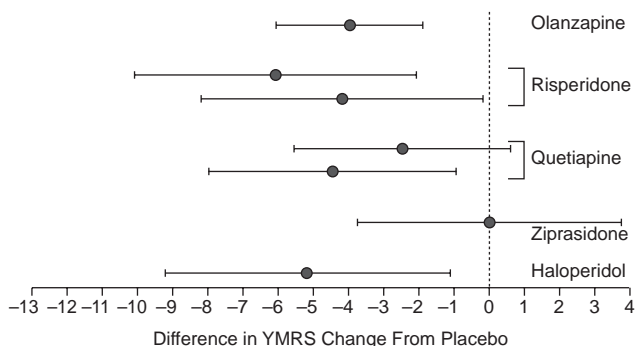
[a]Reprinted with permission from Perlis et al.[8] Bars represent 95%
    confidence intervals.
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 3. Mean Young Mania Rating Scale Score Changes:
Atypical Antipsychotics Versus Mood Stabilizers[a]

[a]Adapted with permission from Scherk et al.[9]
Abbreviation: SMD = standard mean difference.

some were based in the United States; and titration schedules varied. Another limitation of this meta-analysis is that differences may exist in time to onset of action, but time to onset is difficult to compare between studies because different assessment points were used. The same limitations are apparent in the subsequent meta-analysis of Scherk et al.[9]

Atypical Antipsychotics Versus Other Medications

Atypical antipsychotics have been compared with mood stabilizers and haloperidol, as well as with each other for the treatment of acute mania. For comparison against mood stabilizers, Scherk et al.[9] analyzed 5 studies that compared efficacy among olanzapine, quetiapine, or risperidone and lithium or divalproex (Figure 3).[10–14]

Two studies compared olanzapine and divalproex.[10,11] In a 12-week, double-blind, parallel-group, multicenter study,[11] participants with acute mania were randomly assigned to treatment with divalproex (N = 63) or olanzapine (N = 57). No significant differences were found between the medications on the primary outcome measure, the MRS (divalproex: mean = –14.8, olanzapine: mean = –17.2).

Three studies compared atypical antipsychotics to lithium or haloperidol.[12–14] Berk et al.[12] compared the efficacy of olanzapine with that of lithium in patients with mania (N = 30). The 4-week, randomized, double-blind, controlled trial found no significant differences between agents on any of the primary outcome measures. However, olanzapine-treated patients showed significantly more improvement on the Clinical Global Impressions-Severity of Illness scale (CGI-S) at week 4 (p = .025). Bowden et al.[13] conducted a 12-week, randomized, double-blind multicenter trial of quetiapine or lithium compared with placebo for mania. Both quetiapine and lithium were superior to placebo in primary and secondary outcome measures; however, no significant differences were found between the
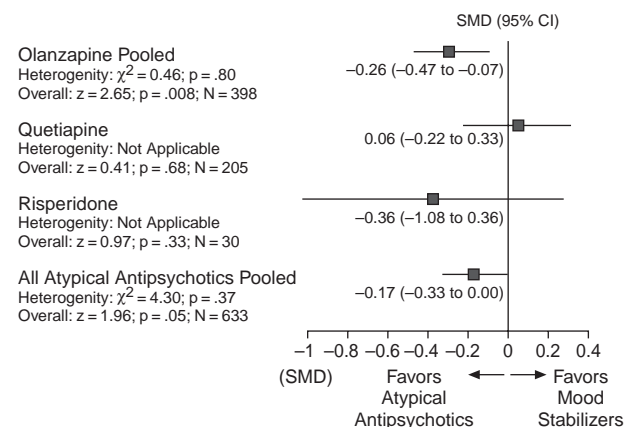
2 medications. A 28-day, randomized, double-blind, controlled trial[14] also found similar efficacy for risperidone compared with both lithium and haloperidol for acute mania.

Few studies directly compare atypical antipsychotics for the treatment of mania. One randomized, double-blind, multicenter study[15] compared olanzapine (5–20 mg/day; N = 165) and risperidone (1–6 mg/day; N = 164) monotherapy for acute manic or mixed episodes over 3 weeks. Anticholinergic medication (benztropine mesylate, up to 2 mg/day) was also allowed to control extrapyramidal symptoms (EPS), and lorazepam was allowed for severe agitation. The YMRS was used as the primary measure of efficacy, and the 21-item Hamilton Rating Scale for Depression (HAM-D-21), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions-Bipolar version (CGI-BP) severity of illness scale were used as secondary measures. The study found no significant differences between the medications on the primary or secondary measures from baseline to endpoint, although secondary measures showed that olanzapine may be slightly more beneficial than risperidone for depressive symptoms, as olanzapine-treated patients had significantly more improvement across study visits in both CGI-BP and HAM-D-21 scores (p = .026 and p = .040, respectively). In addition, significantly more patients in the olanzapine group completed the study (78.7% vs. 67.0%, p = .019). However, safety and tolerability varied between treatments.

Safety and Tolerability of Atypical Antipsychotics

Efficacy is not the only factor that should be considered when deciding on treatment for mania; safety and tolerability are equally important. A medication may be extremely efficacious but not well tolerated and, therefore, not clinically useful because the patient may discontinue

Table 1. Summary of Side Effects With Atypical Antipsychotics[a,b]

Medication	Extrapyramidal Side Effects/ Tardive Dyskinesia	Prolactin Elevation	Weight Gain	Glucose Abnormalities	Lipid Abnormalities	Sedation	Hypotension	Anticholinergic Side Effects
Clozapine	0	0	+++	+++	+++	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	0
Olanzapine	0	0	+++	+++	+++	+	+	++
Quetiapine	0	0	++	++	++	++	++	0
Ziprasidone	0	+	0	0	0	0	0	0
Aripiprazole	0	0	0	0	0	+	0	0

[a]Reprinted with permission from Weiden and Buckley.[22]
[b]From the American Psychiatric Association.[23]
Symbols: 0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose,
  ++ = sometimes causes side effects at therapeutic dose, +++ = frequently causes side effects at therapeutic dose.

the agent or the clinician cannot optimize the dose. While atypical antipsychotics have fewer side effects than typical antipsychotics, weight gain, glucose dysregulation, and dyslipidemia are among the side effects associated with atypical antipsychotics, and these side effects may lead not only to nonadherence in the short term but, if the patient does continue to take the drug, to medical consequences over time.[16,17] Other adverse events such as sedation, EPS, and elevated prolactin levels may also occur.

Dropout in clinical trials. In the Scherk et al. meta-analysis,[9] dropout due to adverse events with atypical antipsychotic monotherapy did not differ between agents and was similar to that of placebo, lithium, and divalproex. However, dropout due to adverse events was lower for atypical antipsychotics than for haloperidol (relative risk = 0.56, 95% CI = 0.34 to 0.94, p = .03); this result is consistent with the APA recommendation favoring atypical antipsychotics over typical antipsychotics because of better tolerability. Overall, dropout due to adverse events with the combination of a mood stabilizer and an atypical antipsychotic did not differ from that of a mood stabilizer plus placebo.

Extrapyramidal symptoms. Side effects such as dystonia, akathisia, dyskinesia, and parkinsonian-like symptoms are associated with antipsychotic medications.[18] While rates of EPS are generally less with atypical antipsychotics than with typical antipsychotics, risperidone, aripiprazole, and ziprasidone demonstrated a higher incidence of EPS compared with placebo.[9]

Khanna et al.[19] examined the safety and efficacy of risperidone for treatment of acute mania and found that more risperidone-treated patients experienced EPS than placebo-treated patients. Although the EPS were mild to moderate in severity, 36% of risperidone-treated patients were given antiparkinsonian medications versus 6% of placebo-treated patients. Keck et al.[20] assessed the safety and efficacy of aripiprazole for manic and mixed episodes and observed higher rates of EPS for aripiprazole-treated patients than for placebo-treated patients. The most common EPS were akathisia, hypertonia, and tremor. Potkin et al.[21] measured the efficacy and tolerability of ziprasidone in patients with manic or mixed episodes and found that

dropout due to adverse events was numerically but not statistically significantly higher for ziprasidone-treated patients than for placebo-treated patients (ziprasidone: 5.8%, placebo: 1.5%, p = .20).

Long-term adverse effects. When choosing a medication that may be continued for maintenance treatment, such as those that treat bipolar disorder, clinicians also need to consider long-term adverse effects. For example, a patient may experience continued weight gain, which, over time, may be associated with metabolic syndrome, cardiovascular disease, and diabetes mellitus.

Adverse effects vary substantially between atypical agents (Table 1).[22,23] Olanzapine and clozapine are associated with the highest risk of weight gain, hyperglycemia, and dyslipidemia.[24–26] The relationship between these medications and weight gain has been examined in several studies.[11,15,27,28] For example, Kluge et al.[27] conducted a randomized, double-blind, parallel study that examined eating habits of 30 patients given either clozapine or olanzapine. The study found that these patients experienced food cravings, binge eating, or both, which became more prevalent in both groups over time. However, olanzapine-treated patients were more likely to experience food cravings at any given time during the study than clozapine-treated patients (48.9% vs. 23.3%, respectively, p = .068). In addition, Zajecka et al.[11] found that olanzapine-treated patients experienced significantly more weight gain than divalproex-treated patients (4.0 kg vs. 2.5 kg, respectively, p < .05).

Other adverse effects often associated with particular atypical antipsychotics include hyperprolactinemia and EPS with risperidone (especially at higher doses) and prolonged heart rate corrected QT interval with ziprasidone.[24] Clozapine is associated with greater risk for agranulocytosis, postural hypotension, sedation, seizures, and antimuscarinic symptoms.

Long-term adverse effects should be considered on an individual basis. For instance, clinicians may avoid prescribing medications that have a high risk of weight gain for patients who are overweight or have a personal or family history of diabetes, obesity, or hyperlipidemias.[26,29,30]

OTHER CLASSES OF
MEDICATIONS FOR ACUTE MANIA

Mood Stabilizers

Lithium. Lithium was approved for the treatment of acute mania in 1970 and for the maintenance treatment of mania in 1974. Since its approval, lithium has been considered the "gold standard" of treatment for bipolar disorder.[31] Although the use of lithium in North America has declined over recent years, this lack of use may be based on opinion and not evidence,[32] as a vast amount of studies support its continued use for bipolar disorder, especially for the prevention of manic or hypomanic relapse.[33] Common side effects of lithium include nausea, changes in appetite, mild diarrhea, hand tremors, dizziness, excess thirst, and excess urination.[34]

Divalproex. Divalproex, like lithium, is recommended by the APA[6] as a first-line treatment for acute mania. Divalproex is similar to lithium in efficacy and is often given to patients who do not respond to or cannot tolerate treatment with lithium. Divalproex may also have a faster time to onset than lithium.[35] However, divalproex is not FDA-approved for maintenance treatment of bipolar disorder or for acute depression. Weight gain may be a side effect of divalproex,[36] and other common side effects of divalproex include nausea, drowsiness, and dizziness.[37]

Carbamazepine. Over the last 3 decades, carbamazepine has shown efficacy for acute and maintenance treatment of bipolar disorder. In 2004, an extended-release formulation of carbamazepine was approved by the FDA for acute treatment of manic and mixed episodes.[38,39] Weisler and colleagues[40,41] conducted 2 randomized, double-blind, placebo-controlled, multicenter trials of the extended-release carbamazepine formulation. Both trials found carbamazepine to be more effective than placebo for treating acute mania. To further analyze the efficacy and safety of carbamazepine, Weisler et al.[42] used the pooled results of these 2 trials and used the YMRS, the CGI-S, the CGI-Improvement (CGI-I) scale, and the HAM-D. At endpoint, both patients with manic and mixed episodes who had received carbamazepine showed significant mean improvements on the YMRS compared with placebo ($p < .0001$ and $p < .01$, respectively). In addition, carbamazepine-treated patients with manic or mixed episodes improved significantly on the CGI-S and the CGI-I, and carbamazepine-treated patients with mixed episodes showed a mean improvement of 4.8 points on the HAM-D versus 2.3 points with placebo ($p < .05$). Dizziness, sedation, rash, dry mouth, upset stomach, and constipation are common side effects of carbamazepine.[43]

Oxcarbazepine. Oxcarbazepine, a carbamazepine derivative, is similar in structure to carbamazepine but has milder side effects and fewer drug interactions. Few studies[44,45] have examined the efficacy of oxcarbazepine for adults with bipolar disorder, and the majority of recent studies have methodological flaws such as small sample sizes and inadequate follow-up periods. However, a large double-blind, randomized, placebo-controlled trial[46] examined the efficacy and safety of oxcarbazepine in children and adolescents with bipolar disorder (N = 116). The study found that patients taking oxcarbazepine had no change in YMRS scores compared with placebo after 7 weeks of treatment (adjusted mean change: oxcarbazepine = –10.90, placebo = –9.79). In addition, dropout due to adverse events was considerably higher for oxcarbazepine-treated patients than for placebo-treated patients (11 vs. 2). Common side effects of oxcarbazepine include headache, dizziness, sedation, unsteady or irregular gait, tremor, fatigue, double or abnormal vision, nausea, vomiting, stomach pain, and indigestion.[47]

Anticonvulsants

In recent years, much interest has been expressed in the efficacy of novel or third-generation anticonvulsants for the treatment of mania. Yatham et al.[48] conducted a comprehensive literature review of open-label and double-blind studies measuring the efficacy of the third-generation anticonvulsants lamotrigine, gabapentin, topiramate, tiagabine, and zonisamide. The review[48] found that multiple trials support the efficacy of lamotrigine for acute and long-term treatment of bipolar depression as well as for rapid-cycling bipolar II disorder, but lamotrigine is not efficacious for treatment of acute mania. Gabapentin shows efficacy as adjunct treatment but does not show efficacy for acute mania. Topiramate has shown efficacy for acute mania in open trials, but more conclusive data are needed. Lastly, the review[48] only found 1 trial for zonisamide, which needs further study, but the existing data do not demonstrate efficacy of tiagabine for treatment of acute mania.

CONCLUSION

Guidelines are based on scientific evidence and expert opinion and should be consulted for treatment of bipolar mania, but they are often limited by the type of evidence available and the difficulty in weighting efficacy, tolerability, and safety. All of the atypical antipsychotics except clozapine are FDA-approved for the treatment of acute mania, as are lithium, chlorpromazine, divalproex, and carbamazepine. Most atypical antipsychotics appear to be similar in their acute efficacy when compared to placebo and are also similar in efficacy to lithium, divalproex, and haloperidol; however, some may have a faster onset of action than older agents. Carbamazepine extended-release is more effective than placebo for treatment of mania. Novel anticonvulsants have not been proven effective for treatment of mania. Clinicians should consider not only efficacy but also tolerability and safety when deciding on treatments for mania. Additionally, long-term adverse

effects should be weighed when choosing a medication for acute therapy because the medication may be continued during maintenance treatment.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), carbamazepine (Tegretol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), quetiapine (Seroquel), risperidone (Risperdal and others), tiagabine (Gabitril), topiramate (Topamax), ziprasidone (Geodon), zonisamide (Zonegran and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, benztropine, chlorpromazine, clozapine, divalproex, gabapentin, haloperidol, oxcarbazepine, tiagabine, topiramate, and zonisamide are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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