Safety of Available Agents Used to Treat Bipolar Disorder: Focus on Weight Gain

Charles B. Nemeroff, M.D., Ph.D.

Background: Pharmacotherapeutic management of bipolar disorder has advanced considerably since the introduction of lithium therapy nearly 50 years ago. The sizable percentage of patients who do not respond adequately to lithium and/or are intolerant to its side effects has served as an impetus for identifying alternative pharmacotherapeutic agents. Recent advances in the understanding of the neurotransmitter systems and their receptors as it applies to treatment of bipolar disorder has, in part, led to progress in delineating applications of anticonvulsant/antiepileptic drugs (AEDs) in this area. Although the efficacy of many drugs has been evaluated in patients with this disorder, medication tolerability and adherence issues related to unfavorable side effect profiles are substantial impediments to the development of novel pharmacotherapies. The potential for excessive weight gain as a side effect of certain psychopharmacologic agents remains a concern to both clinicians and patients.

Method: English-language literature from 1985–2001 in MEDLINE was searched for the terms *bipolar disorder, anticonvulsant, antiepileptic, lithium, antipsychotic, weight,* and *compliance*. This article reviewed current therapeutic options for bipolar disorder, including newer AEDs and atypical antipsychotic drugs, with emphasis on the issue of weight gain and possible approaches to minimizing this risk.

Results: Certain newer AEDs are characterized by more favorable safety and tolerability profiles that include weight loss as a desirable side effect. Because bipolar disorder is associated with unacceptably high rates of relapse, recurrence, and morbidity, the concept of pharmacotherapeutic efficacy logically not only includes symptom relief but also necessarily encompasses issues related to regimen tolerability and adherence.

Conclusion: There is a need for guidelines to help physicians carefully formulate and individualize management plans to reach safe, effective, and cost-efficient patient outcomes. Monitoring the weight of patients with bipolar disorder and educating them regarding this issue should be standard components of any treatment plan.

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Corresponding author and reprints: Charles B. Nemeroff, M.D., Ph.D., Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1639 Pierce Dr., Ste. 4000, Atlanta, GA 30322 (e-mail: cnemero@emory.edu).

Undoubtedly, the treatment of patients with bipolar disorder has advanced substantially over the half century since the advent of lithium pharmacotherapy. In addition to traditional lithium therapy, anticonvulsant/antiepileptic drugs (AEDs) and atypical antipsychotic drugs now are also being used to treat this disorder. Despite a growing drug armamentarium, clinicians are often faced with lower-than-desired efficacy in the practice setting. In light of the inherently high relapse and recurrence rates and the substantial morbidity associated with bipolar disorder, all potential risks to clinical management success should be identified and scrutinized. Medication tolerability, drug-drug interactions, toxicity, and adherence issues related to unfavorable side effect profiles, such as excessive weight gain, often surface and sometimes completely undermine treatment success.

The potential for excessive weight gain as a side effect of certain psychotherapeutic agents used in the management of bipolar disorder has remained an important concern to both clinicians and patients over the years (Table 1). In addition to the well-known risks of physical morbidity and mortality, such as lipid, glucose, and blood pressure increases and cardiovascular risk, being overweight and gaining weight have psychosocial consequences.[1] With obesity representing a public health concern of near-critical proportions in this country, the potential risk of additional weight gain in already medically challenged populations is of great concern.[2] Experts cite from clinical experience that patients with mental illness often gain

Table 1. Issues and Considerations: Pharmacotherapy-Related Weight Gain in Bipolar Disorder

An important clinical management dilemma
Societal view of obesity
Psychosocial sequelae
Physical morbidity/mortality risks, eg, cardiovascular and cerebrovascular disease risk, diabetes risk
Comorbid weight gain risks
Weight loss is often difficult
Potential relation to remitted depression
No standard evaluative criteria
Obesity not fully understood
Long-term effects often underestimated
Poor individual predictive value
Management complacency
Relationship to regimen adherence
Need for drugs with more favorable safety profiles

enough weight secondary to psychotherapeutic medications to result in adverse health effects and loss of this weight often proves difficult.[3] In addition, data suggest that weight gain may be associated with remission of pharmacologically treated depression symptoms in bipolar patients.[4]

English-language literature from 1985–2001 in MEDLINE was searched for the terms *bipolar disorder, anticonvulsant, antiepileptic, lithium, antipsychotic, weight,* and *compliance*. This article presents an overview of current options for treating bipolar disorder with the objective of maximizing therapeutic success and minimizing therapy-associated side effects.

TRADITIONAL LITHIUM PHARMACOTHERAPY IN BIPOLAR DISORDER

Although it remains first-line treatment, lithium presents issues of efficacy and tolerability that are of major concern, with estimates of overall unsatisfactory clinical response in approximately 50% of bipolar patients.[5] Issues facing long-term clinical management of bipolar disorder with lithium therapy are particularly significant, considering that, at the time of preparation of this article, it is the only medication approved by the U.S. Food and Drug Administration (FDA) for long-term treatment of bipolar disorder, and drug tolerability and adherence greatly impact the course of bipolar disorder. Lithium prophylaxis is accompanied by the expectation of common side effects such as fine hand tremor, polyuria and polydipsia, hypothyroidism, and weight gain.[6,7] Failure to adhere to lithium prophylaxis is associated with high rates of bipolar illness recurrence, calculated to be 28 times greater than would be expected from the natural cycling frequency in untreated bipolar disorder, and a marked increase in suicide risk.[8] Large data cohorts of bipolar patients characterize lithium usage as sporadic rather than continuous, as is the therapeutic recommendation.[9]

Weight gain is an issue closely linked to lithium regimen noncompliance.[7] Lithium-induced weight gain is cited as one of the primary reasons patients stop taking the drug, even when they are experiencing favorable symptom relief.[3] Excessive weight gain related to lithium therapy, amounting to more than 10 pounds (4.5 kg) over what can be explained by fluid retention, is experienced by approximately 25% of patients.[7] In one study, up to 30% of lithium-treated patients became obese, a percentage that exceeds the obesity prevalence for the general population 3-fold.[8] In light of these statistics and the fact that lithium prophylaxis nonadherence is estimated in some reports to exceed 50%,[7] other avenues of pharmacologic management need to be examined.

ANTICONVULSANT/ANTIEPILEPTIC DRUGS IN BIPOLAR DISORDER

Recent advances in the neurobiology of bipolar disorder have led to the identification of certain AEDs for use in this therapeutic area. Practice experience and some controlled data suggest that among patients with rapid cycling, mixed states, and/or comorbid substance abuse disorder, therapy with AEDs has emerged as an important part of the treatment armamentarium.

The anticonvulsant valproate, indicated for the acute treatment of manic episodes associated with bipolar disorder, is effective for many patients who either do not respond to or cannot tolerate therapy with lithium or carbamazepine, as well as for patients with mixed or dysphoric mania or those with rapid-cycling bipolar disorder.[10] In addition to monotherapy, valproate may be administered in combination with lithium.[11] Clinicians need to be cognizant of and vigilant about adverse events such as hepatic failure (in children), thrombocytopenia (rare), and transaminase elevations. The more common side effects include nausea, vomiting, tremor, somnolence, and weight gain.[12,13] Although valproate is cited as being generally well tolerated, some clinicians have commonly cited therapy-related weight gain as a factor in treatment discontinuation.[3,8,14] Many patients may gain up to 44 pounds (19.8 kg) during valproate therapy, depending on the length of the treatment.[15] Recent data from a double-blind, controlled trial examining 1-year valproate therapy for bipolar disorder reported that approximately one quarter of valproate-treated patients experienced significant weight gain compared with the placebo group ($p < .001$).[13] In addition, with concurrent lithium therapy, the potential of additive weight gain with the 2 agents cannot be discounted.

Carbamazepine is another AED with evidence demonstrating comparable efficacy to that of lithium and prophylactic effects in bipolar disorder management.[16–21] In addition to combination therapy with lithium, carbamazepine monotherapy for difficult-to-treat patients (i.e.,

lithium-resistant individuals with mood-incongruent features) is common.[14] Although carbamazepine is currently not indicated for bipolar disorder management, the literature and clinical practice document efficacy for this application. Although carbamazepine may be less likely to result in therapy-induced weight gain than either lithium or valproate, other adverse events may be of concern for many patients taking this agent (e.g., blood dyscrasias, sedation, hepatic enzyme autoinduction, gastrointestinal symptoms).[8,14,22] Oxcarbazepine, with significantly fewer side effects and drug-drug interactions than carbamazepine, appears also to possess efficacy in the treatment of bipolar disorder.[22–25]

Gabapentin, currently indicated as adjunctive therapy in the treatment of partial seizures,[26] was suggested to be safe and efficacious in a number of small trials as adjunctive treatment of mania, hypomania, and resistant bipolar disorder states.[27–31] However, other studies have obtained discordant results with both monotherapy and adjunctive therapy.[32,33] A double-blind, placebo-controlled trial of adjunctive gabapentin in bipolar I patients did not reveal any efficacy in outpatients.[33] In the present context, it is important to note that in studies of gabapentin for seizure disorders, weight gain is documented as a common side effect when gabapentin is administered both as add-on therapy and as monotherapy.[34,35] Evidence of approximately 25% of subjects gaining more than 10% of their baseline weight has been recorded,[34] as well as a gabapentin dose-related weight gain.[35]

Tiagabine, a novel antiepileptic thought to enhance the activity of γ-aminobutyric acid (GABA), is indicated for adjunctive treatment of partial seizures.[36] Use of tiagabine in bipolar disorder has been described in a limited number of publications. An open trial[37] comprising 8 acutely manic DSM-IV bipolar I patients was reported in which 2 patients received tiagabine monotherapy and 6 received add-on tiagabine treatment. After 14 days of treatment, none of the patients showed prominent relief of manic symptoms, and 2 patients suffered pronounced side effects of nausea, vomiting, and generalized tonic-clonic seizure.[37] A small case series[38] included 3 patients, 2 with bipolar disorder and 1 with schizoaffective disorder, bipolar type. Improvement of bipolar and schizoaffective symptoms with low-dose tiagabine adjunctive therapy was reported in this study. Because of discordant results and insufficient data, more studies are needed to determine if tiagabine is safe and effective for bipolar patients.

Levetiracetam, a novel antiepileptic, is indicated as adjunctive therapy in the treatment of partial-onset seizures.[39] The safety and efficacy of levetiracetam for bipolar patients remain obscure.

Lamotrigine trials in bipolar disorder have shown some efficacy in refractory bipolar states.[40–44] Thirty-one patients with refractory bipolar and unipolar mood disorders participated in a double-blind, randomized, crossover series of 6-week monotherapy treatments with lamotrigine, gabapentin, and placebo.[32] Lamotrigine, initiated at 25 mg daily, was titrated weekly by 50- to 200-mg increments to a mean dose of 274 mg by week 6. Gabapentin was initiated at 900 mg daily and titrated weekly up to a mean daily dose of 3987 mg. Response rates, measured with the Clinical Global Impressions-Bipolar (CGI-BP) scale,[45] improved 52% for lamotrigine, 26% for gabapentin, and 23% for placebo. Studies evaluating the use of lamotrigine in the treatment of bipolar depression[41,43] and rapid-cycling bipolar disorder[46–48] suggest particular efficacy in the former and some efficacy in the latter. Weight gain does not appear to be an issue with this agent. Ultimately, the benefits must be weighed against potential side effects such as Stevens-Johnson syndrome, though rare, which do occur with lamotrigine administration.[40,42,43,49,50]

Topiramate is FDA-indicated for use as adjunctive therapy in the treatment of partial-onset seizures, generalized tonic-clonic seizures, and Lennox-Gastaut syndrome in adults and in pediatric patients aged 2 to 16 years; current evidence suggests that this AED also may be effective as a mood stabilizer in bipolar patients unresponsive to traditional agents.[51–55] In addition to its suggested utility as either adjunctive therapy or monotherapy in manic, hypomanic, and cycling-mood instability in bipolar disorder, topiramate is not associated with serious side effects or weight gain. Common side effects are cognitive and may include language problems and difficulty with concentration and/or attention.[56] Factors that may influence the occurrence of side effects include dose titration, adjunctive and combination therapy, and diagnosis. The results of a small, open-label pilot study[57] involving the use of topiramate monotherapy in 10 hospitalized acutely manic patients demonstrate an average 50% response rate within a mean duration of treatment of 16 days. Dosing was initiated at 50 mg/day and titrated upward by 50-mg increments every 3 days until an optimal dosage was determined (maximum 1600 mg/day). Adverse events that occurred in at least 10% of the patients were paresthesias, decreased appetite, nausea, and constipation.

Twenty-seven women with cycling bipolar-mood instability and a history of psychotropic-induced weight gain over the course of the preceding 24 months were treated with lithium or divalproex.[53] Adjunctive topiramate therapy was initiated at 25 mg/day and increased in 25-mg increments every 5 to 7 days until clinical response or tolerability was achieved. The maximum dosage was 150 mg/day. By 12 weeks of well-tolerated therapy, 15 patients had improved significantly; in addition, 9 women experienced a weight loss of more than 5% during 16 weeks of therapy.[53]

An open-label, prospective trial[52] of topiramate as adjunctive therapy to preexisting psychotropic regimens (mood stabilizers, antipsychotics, antidepressants, and

Table 2. Change in Body Weight: Bipolar Patients Receiving Adjunctive Topiramate[a]

		Weight (kg)		Weight Loss (kg)	
Time of Evaluation	N	Mean (SD)	Range	Mean (SD)	% Change
Study entry[b]	53	92.2 (26.3)	54–171	NA	NA
4 weeks[b,c]	50	91.1 (27.0)	53–171	–0.7 (1.9)*	–0.1
10 weeks[b,c]	50	91.1 (27.0)	51–165	–1.6 (2.9)**	–1.7
6 months[c]	37	94.4 (26.9)	53–162	–4.7 (5.9)**	–4.8
1 year[c]	37	93.0 (26.5)	49–156	–6.2 (7.5)**	–6.2
Last evaluation[b,c,d]	53	87.7 (25.1)	51–156	–4.5 (6.7)**	–4.9

[a]Reprinted from McElroy et al.,[52] with permission.
[b]Weight missing for 1 patient at study entry, 4 patients at 4 weeks, 4 patients at 10 weeks, and 1 patient at last evaluation.
[c]Last-observation-carried-forward method (intention-to-treat analysis).
[d]Mean (SD) of 214.2 (169.6) days.
*p < .05; **p < .001.

Table 3. Change in Body Mass Index (BMI): Patients Receiving Adjunctive Topiramate[a]

		BMI		Change in BMI	
Time of Evaluation	N	Mean (SD)	Range	Mean (SD)	% Change
Study entry[b]	52	32.3 (9.6)	20–61	NA	NA
4 weeks[b,c]	49	31.3 (8.8)	19–56	–0.9 (4.7)	–2.9
10 weeks[b,c]	49	32.1 (9.7)	19–59	–0.6 (1.0)*	–1.7
6 months[c]	37	33.3 (9.9)	19–58	–1.6 (1.9)*	–4.7
1 year[c]	37	32.7 (9.8)	19–56	–2.2 (2.5)*	–6.3
Last evaluation[b,c,d]	52	30.7 (9.2)	19–56	–1.6 (2.3)*	–5.0

[a]Reprinted from McElroy et al.,[52] with permission. BMI = weight in kg/height in m^2.
[b]BMI missing for 2 patients at study entry, 5 patients at 4 weeks, 5 patients at 10 weeks, and 2 patients at last evaluation.
[c]Last-observation-carried-forward method (intention-to-treat analysis).
[d]Mean (SD) of 214.2 (169.6) days.
*p < .001.

benzodiazepines) evaluated 56 patients diagnosed with bipolar disorder or schizoaffective disorder. Prior to the addition of topiramate, patients either did not tolerate or exhibited inadequate responses to their mood-stabilizing regimens. Twenty-five milligrams of topiramate twice daily was added and titrated upward in 50-mg increments every 7 days until improvement was seen or a dosage of 400 mg/day was reached. Of the 30 patients who were treated for manic symptoms, 63.3% were much or very much improved (based on the CGI-BP scale) by week 10. Significant decreases of initial Young Mania Rating Scale scores were also displayed at week 10.[52] At the end of 10 weeks of acute topiramate therapy, mean weight loss was 1.6 kg (3.5 lb) and mean change in body mass index (BMI) was –0.6 (Tables 2 and 3). This weight loss and decrease in BMI continued to the last evaluation period (mean = 294.6 days). Two placebo-controlled, double-blind trials of topiramate monotherapy for patients with acute mania have now been completed. No efficacy of topiramate was revealed in Ortho-McNeil unpublished observations.

The precise mechanisms responsible for topiramate-related weight reduction remain to be established. It is interesting to note that individuals described as being more obese lose the most weight on topiramate therapy, which is consistent with data reported in the epilepsy literature.[58] In one study of bipolar patients treated with topiramate as add-on therapy (N = 18), individuals with BMI scores of at least 30 lost more weight (almost 10.2 lb [4.6 kg]) than did those with BMI scores under 30, who had lost 7 lb (3.2 kg) by the 5-week follow-up visit.[55] This weight loss was maintained, and further reduction was observed in the follow-up of patients (up to 10 months in some individuals).[54]

ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DISORDER

Atypical antipsychotic agents, characterized by 5-HT_2- and D_2-receptor antagonist properties, are recent options for adjunctive treatment of or monotherapy for bipolar disorder. Included in this class are clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone. Of these, only olanzapine,[59,60] risperidone,[61,62] aripiprazole, and ziprasidone[63] have been studied in controlled clinical trials for the treatment of bipolar mania. These agents have been shown to be superior to placebo (olanzapine, aripiprazole, ziprasidone), lithium (risperidone, olanzapine), and haloperidol (risperidone, aripiprazole). Risperidone combination therapy with a mood stabilizer (lithium or valproate) has also been shown to be superior to mood-stabilizer monotherapy.[61] Data from open-label studies support the efficacy of clozapine in the treatment of acute bipolar mania,[64,65] and a case report suggests that the addition of quetiapine to the treatment regimen may be useful in treatment-resistant bipolar mania.[66] One retrospective, naturalistic comparison of 50 treatment trials in patients with bipolar disorder I indicated that the efficacy of clozapine, olanzapine, and risperidone in improving CGI scores may be comparable.[67] Although further studies may serve to differentiate the relative antimanic, antidepressive, antipsychotic, and mood-stabilizing properties of the atypical antipsychotics, the major difference among them appears to lie more in their side effect burden than in their efficacy, a factor that will have an impact on treatment adherence.

Overall, atypical antipsychotic agents have generally better side effect profiles than do conventional antipsychotics. Side effects of concern include extrapyramidal symptoms (EPS), sedation, sexual dysfunction, and weight gain. In addition, evidence is mounting that antipsychotic treatment may impair glucose tolerance. Although this propensity varies among antipsychotics, a causative effect has been reported with chlorpromazine,

clozapine, and olanzapine. At its most serious, it can cause diabetic ketoacidosis, which can lead to death.[68,69]

Some atypical antipsychotics have been reported to be associated with significant weight gain. The degree of weight gain varies from agent to agent and may be dependent on the effect of the agent on specific neurotransmitter receptors.[70,71] A meta-analysis of 81 articles[72] that included data on the effects of antipsychotic agents on body weight indicated that among the newer atypical antipsychotics, clozapine had the greatest mean weight gain (4.45 kg [9.89 lb]), followed by olanzapine (4.15 kg [9.22 lb]), risperidone (2.10 kg [4.67 lb]), and ziprasidone (0.04 kg [0.09 lb]) over a 10-week period on standard drug doses. Thus, the newest generation of antipsychotic agents appears to have a more favorable EPS profile as well as more favorable non-extrapyramidal effects, such as weight gain, than do older agents. Though ziprasidone is the only agent that has been shown to cause little or no weight gain, it has been reported to prolong the QT interval, although the clinical effect of this is debated.[73] Aripiprazole also appears to be weight neutral.

The causes, mechanisms, and risk factors underlying weight gain, diabetes risk, and complications with atypical antipsychotics are not clear and remain to be investigated. More long-term and rigorous data are needed to completely assess their impact on both weight gain and diabetes risk. In a review of seven 1-year trials with risperidone, Brecher and Burks[74] reported that weight gain with risperidone is dose related and has a tendency to level off with time.

EXCESSIVE WEIGHT GAIN: CLINICAL MANAGEMENT CONSIDERATIONS

Obviously, weight gain is almost always the consequence of a complicated interplay of many biological, social, and psychological factors.[75] Often, in cases with multiple-drug regimens, long-term cumulative effects on weight gain are underestimated.[3] Definitively predicting who will or will not gain excessive weight in response to certain pharmacologic regimens, as well as how much weight will be gained, is not possible at the present time. Unfortunately, when symptom management is satisfactory to both patient and clinician, a certain degree of complacency may exist with regard to recognizing and regularly monitoring other important health parameters such as weight gain.[3]

The acceptance of excessive weight gain as a necessary consequence of clinical psychiatric improvement should be abandoned,[75] and the potential therapy-induced risks of weight gain (diabetes, coronary heart disease, high blood pressure) should be considered when the comprehensive treatment plan is formulated. There is clearly a need to be vigilant about these issues when clinicians prescribe olanzapine and clozapine. Practitioners should be encouraged to look to emerging treatment regimens that, in addition to having clinical efficacy, have safety profiles that include benefits such as weight loss that will increase the potential for patient adherence.

Adherence Issues

In psychiatry, the clinical management of chronic mental illness is challenging because of cognitive impairment, adverse side effects of many medications, and patient fears of potential social stigmatization. Nonadherence in chronic mental illness—where relapse, recurrence, and morbidity are significant—plagues patients and practitioners alike. Overall, psychopharmacologic nonadherence in bipolar disorder is a major factor in poor outcome. In a study of more than 100 patients,[76] a total medication nonadherence rate of 64% was reported across varying regimens prior to inpatient admission for manic symptoms. Symptom exacerbation related to therapy nonadherence not only is potentially dangerous to the patient and his/her family, friends, and colleagues but also results in a greater utilization of health care resources.[76,77] Not surprisingly, in one analysis of drug therapy regimens, increased length of hospital stay for acute inpatient mania treatment was found to be related, in part, to medication nonadherence history.[78]

Therapy is often complicated by overall pharmacologic regimen intolerance, leading to subsequent nonadherence. Some side effects, such as excessive weight gain, may cause a reduction in perceived self-worth, whereas others, such as tremor, can be a visible marker of illness. A patient's perceptions about the relative risks and benefits of treatment are cited as a strong determinant of medication regimen adherence, thus highlighting the need for identification and intervention to remedy potential barriers to adherence.[77,79,80] Compared with the degree of neuropsychological impairment, patient attitudes toward medications and their side effects were found to be more clinically relevant in a randomized, controlled trial of adherence to therapy in psychotic patients (N = 74).[79] Patient perceptions with regard to medication, be they accurate or inaccurate, cannot be underestimated for their effects on outcomes. A large longitudinal study of military veterans (N = 1648) demonstrated that patient perceptions regarding dosing (i.e., perceived overmedication) were directly correlated to self-reports of decreased adherence and diminished measures of quality of life.[80]

Clearly, adherence is closely associated with higher ratings on quality-of-life measures and with addressing patient perceptions about their therapeutic regimens, the acknowledgment of their illness, and treatment-related side effect issues.[81] A carefully chosen pharmacotherapeutic agent—one with favorable efficacy and safety profiles—coupled with a well-developed and dynamic management plan is perhaps the best approach to meeting the challenge of long-term medication adherence.[77]

Table 4. Strategies for Successful Pharmacomanagement of Bipolar Disorder

Individualized plan
Proactive perspective
Strategic/collaborative partnership
Health care providers
Patient
Support systems
Continual dialogue
Working set of treatment objectives
Monitoring drug levels/laboratory values
Routine weight recording
Diet and exercise program
Patient education

The Treatment Plan

The overall clinical heterogeneity of bipolar disorder makes it difficult to generalize treatment strategies.[14] Pharmacotherapy practice guidelines can be useful tools in therapeutic decision making,[82] but carefully formulated and individualized management plans are needed in order to reach safe, effective, and cost-efficient patient outcomes (Table 4). The willingness to consider changing a medication regimen that is meeting affective symptom needs, despite side effect experience that is not immediately life threatening, is also a major consideration, especially for patients who have been refractory to previous treatment regimens. Approaching bipolar management from a proactive perspective of a carefully planned strategic partnership between the patient, support systems, and health care providers may help facilitate the much-needed dialogue and care continuum.

Up-front objectives for treatment success and plans for meeting potential obstacles are valuable and connote a positive approach rather than a problem-oriented mission. Preventing and guarding against potential therapy-related weight gain are certainly preferred over dealing with the issue when it has become a serious clinical dilemma.[82] In addition to indicated monitoring of therapeutic drug levels and laboratory values, comprehensive health interventions, such as routine monitoring of weight and an exercise and dietary program including nutritional counseling and eating-behavior analysis, will address potential weight gain and facilitate a higher level of individual wellness.

Commonly cited as a practice standard, patient education also must not be overlooked. In general, the literature[79,81,83,84] demonstrates a relationship between treatment adherence and improvements in patient knowledge, attitude, and satisfaction with medical management. Thus, the treatment plan should strive for long-term management adherence based on a model of active collaboration and an adaptation of therapy that not only meets the patient's needs but also is current with emerging advances in bipolar disorder science reflected in pharmacotherapeutic agents with more favorable safety and efficacy profiles.

SUMMARY

Over the years, as psychopharmacology has advanced, the need to reassess traditional bipolar disorder management has become apparent. Although clinical bipolar disorder management remains complex and challenging, emerging applications of pharmacotherapeutic agents are offering new opportunities for safer and more effective treatment. Thus, further investigation of novel applications of AEDs and the development of new agents are warranted to keep pace with public demands for long-term, tolerable therapy with greater efficacy. Bipolar disorder management is best characterized by a dynamic process between clinicians and patients that provides room for both a spirit of collective creativity in formulating the ideal treatment plan and application of state-of-the-art, evidence-based medicine.

Because symptom recurrence and associated morbidity are high, clinicians need to systematically assess and address all potential barriers to therapy adherence, a major risk factor for bipolar disorder management failure. Nonadherence to psychopharmacologic regimens, often related to intolerable weight gain with lithium, certain atypical antipsychotics, and some AEDs, is a significant clinical dilemma for all concerned. Guidelines are needed with regard to more effective protocols for monitoring patient weight regularly and treating existing therapy-related obesity. Education of patients is essential to the success of treatment. The future of bipolar disorder management holds the promise of safer and more effective therapeutic options with more positive clinical outcomes and more cost-efficient utilization of health care resources.

Drug names: carbamazepine (Tegretol, Epitol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), tiagabine (Gabitril), topiramate (Topamax), valproate sodium (Depacon), ziprasidone (Geodon).

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