Anticonvulsant Use in the Treatment of Bipolar Disorder: A Primer for Primary Care Physicians

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Primary care physicians may be directly or indirectly involved in the management of the bipolar patient. Bipolar affective illness is a chronic, recurrent disorder. Patients, their families and support systems, and the general public can face profound and enduring consequences if the illness is untreated or poorly treated. Consequently, increasing attention has been directed at developing treatment strategies to control symptoms associated with bipolar disorder. While lithium has been the mainstay of treatment for many years, recent investigations have demonstrated the utility of a number of anticonvulsant medications in bipolar disorder. This review will discuss the literature on anticonvulsant efficacy in bipolar disorder in light of the treatment guidelines set forth by the Bipolar Treatment Expert Consensus Panel and the American Psychiatric Association. To orient the clinician, issues related to anticonvulsant use, dosing, adverse effects, and drug interactions are also discussed.

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Primary care physicians are increasingly at the forefront of assessing and managing affective disorders, e.g., depression and bipolar disorders. A prospective evaluation of patients endorsing depressed and/or anxious symptoms in a family practice outpatient setting found that 25% of the cohorts had a bipolar spectrum disorder.[1] These data suggest that primary care physicians may be the first to encounter a patient with bipolar disorder. Effective management of the patient with a major mood disorder often requires a collaborative effort between the primary care physician and psychiatrist. The primary care physician may be instrumental in ensuring psychiatric evaluation and follow-up, may be the first to recognize early signs of recurrence, may detect noncompliance, and may be the primary source to whom patients present when adverse effects of use of mood-stabilizing agents are encountered. This article is written to inform primary care physicians about recent trends in the management of bipolar disorder. In addition to familiarizing the reader with bipolar disorder and its variants, the intent here is to heighten awareness of various treatment alternatives including dosing, potential adverse effects, risks associated with pregnancy and lactation, and possibilities of drug interactions.

DIAGNOSIS AND COURSE

Bipolar disorder is characterized by cycles of manic and depressive episodes. During a "classic" manic episode, the patient's mood is notably elated, euphoric, or irritable for a sustained period of at least 1 week's duration.[2] This is accompanied by at least 3 additional symptoms, including inflated or grandiose self-esteem, decreased need for sleep, increased activity characterized by overt agitation or pursuing goal-directed activities, excessive pursuit of pleasurable activities with potentially dangerous consequences, talking more than usual with rapid and pressured speech, overt distractibility, and flight of ideas or a subjective sense that one's thoughts are racing.[2] Often, patients who are in a manic episode have significantly impaired judgment and can lose touch with reality, i.e., the patient may have delusional beliefs or hallucinations. Manic patients may act impulsively on their beliefs or on poorly thought out plans, for example, taking on tasks that cannot be reasonably managed, abandoning responsibilities, engaging in promiscuous behavior, going on spending sprees, making numerous long distance phone calls, and so on. Such actions can be devastating to the patient and the patient's family and can adversely affect the patient's social and occupational functioning. Often, a patient can incur significant debt, health risks, and legal consequences. Untreated bipolar disorder can result in the patient's death and inadvertent harm to others. When manic patients are so impaired as to pose serious threats to their own safety or that of others, hospitalization is required.

If at least one manic episode has been experienced, the patient is said to have bipolar I disorder. There are syndromal variants in bipolar disorder, which differ in presentation, course, and treatment implications.[3] Hypomania is shorter in duration and generally milder in intensity. Hence, while patients may appear noticeably giddy, happy, energetic, etc., they are not so impaired as to cause significant harm to themselves or others or lose contact with reality. In the course of bipolar disorder, patients usually experience profound periods of depression alternating with manic or hypomanic episodes. Patients who experience recurrent episodes of hypomania and depression, but no manic episodes, are said to have bipolar II disorder.[2] In some cases, patients experience episodes during which criteria are simultaneously met for both depression and mania; they are said to have mixed mania.

The course of bipolar disorder is characterized by a high rate of recurrences.[3,4] Patients vary in terms of the number of cycles that they may experience. Often, a cycle can be precipitated by sleep disturbances, life stresses, noncompliance with mood-stabilizing medications, or alcohol and/or illicit substance abuse. For a group of patients, cycles may occur as frequently as 4 or more times per year, which defines the rapid-cycling variant of bipolar disorder.[2]

Bipolar disorder affects approximately 1% of the population, or nearly 2 million persons.[5] In 1991, bipolar disorder incurred $45 billion in costs: $7 billion for direct patient care, e.g., hospitalizations, medication use, and $38 billion for indirect costs, e.g., loss of wages, loss of work productivity, absenteeism.[6]

The consequences of bipolar disorder can be severe, enduring, and pervasive.[7] Hence, efforts have long been directed at developing effective treatments for this disorder. Lithium carbonate was approved for treatment of mania in 1970 by the U.S. Food and Drug Administration (FDA). Until recently, lithium was considered the mainstay of treatment. However, severe adverse effects, potentially dangerous long-term consequences, and a narrow therapeutic index of safety limit the use of lithium.[4,8,9] Furthermore, there is a subgroup of patients who demonstrate a poor response to lithium treatment.[10,11] The effectiveness of lithium in acute mania and long-term maintenance treatment has been questioned by data on patient refractory rates and relapse rates. It is estimated that only 60% to 80% of patients with bipolar disorder have an adequate response to lithium treatment.[12,13] Among patients with acute mania, lithium appears to be efficacious for patients with "classic" mania. Additionally, lithium is effective for patients with a cycle pattern of mania followed by depression and then euthymia. As many as 30% to 50% of bipolar patients, however, have a cycle pattern of depression followed by mania and then a euthymic period[14,15]; such patients tend to have a poorer response to lithium treatment. Patients with mixed mania,[16–18] rapid

cycling,[19] and/or lacking a familial history of affective disorders[15] are also less likely to respond to lithium.

Relapse rates are high despite compliance with lithium treatment and appear to increase over time. Estimated relapse rates are approximately 40% in the first year post-treatment[20] and 73% in 5 years.[21]

The observations above propelled efforts to develop alternate treatment strategies for bipolar affective illness. The link between anticonvulsants and bipolar disorder emerged, in part, from observations that patients treated with anticonvulsants in early epilepsy trials experienced improvements in mood and general improvements in well-being.[22–30] However, these studies were uncontrolled. The observed mood improvements may have been an artifact of better seizure control and commensurate lifestyle improvements and were not necessarily due to direct anticonvulsant effects. Nonetheless, these findings prompted some of the initial investigations into the possible effects of anticonvulsant use in psychiatric circles.

ANTICONVULSANT EFFICACY IN BIPOLAR DISORDER

Acute Mania

Patients refractory or intolerant to lithium are candidates for treatment with valproate (Table 1). Valproate received FDA approval for the treatment of acute mania in 1995. It is the only anticonvulsant thus far to receive FDA approval for treatment of mania. In 2 well-conducted, placebo-controlled, double-blind studies, valproate has been demonstrated to be more effective than placebo in acute mania.[31,32] No significant differences were found in effectiveness between lithium-treated and valproate-treated groups when the latter was compared with a matched lithium-treated group.[31] Subject dropout rates were higher for the lithium-treated group compared with the valproate-treated group, suggesting that valproate was better tolerated.[31]

Alternatively, carbamazepine has demonstrated some promise in the treatment of acute mania.[33] Acutely manic patients treated with carbamazepine demonstrated significant improvements compared with placebo controls; however, lower response rates were obtained with carbamazepine than with lithium.[34,35]

Preliminary evidence suggests that lamotrigine may also have a role in acute mania. The effectiveness of lamotrigine as an adjunctive agent in acute mania was suggested by case reports and a small open-label study (N = 36).[36–38] In the open study, 60% of patients demonstrated a significant reduction in manic symptom severity as quantified on standardized psychiatric rating scales.[38]

Inconsistent, although promising, results were obtained in uncontrolled case reports,[39,40] retrospective chart reviews,[41,42] and open case series[43,44] examining gabapentin adjunctive therapy in acute mania. One open-label

Table 1. Treatment Guidelines For Managing Bipolar Disorder

Condition	First-Line Treatment	Second-Line Treatment	Third-Line Treatment
Acute mania			
"Classic"	Lithium	Valproate	Carbamazepine or lithium + valproate
Mixed	Valproate	Lithium or carbamazepine	Lithium + valproate
Rapid cycling	Valproate	Carbamazepine	Lithium + valproate or lithium + carbamazepine
Bipolar depression	Lithium	Carbamazepine	Lamotrigine ?; gabapentin ?
Mania and mixed episodes refractory to			
Lithium	Replace with or add valproate		
Valproate	Replace with or add lithium		
Carbamazepine	Replace with lithium or valproate		
Mania and mixed episodes partially responsive to			
Lithium	Add valproate or carbamazepine		
Valproate	Add lithium		
Carbamazepine	Add lithium		
Long-term prophylaxis			
"Classic"	Lithium	Valproate	
Rapid cycling	Valproate	Carbamazepine	Lithium alone or combined with valproate or carbamazepine

study found that gabapentin (dose range, 1600–4800 mg/day) added to the preexisting treatment of 8 (88.9%) of 9 acutely manic patients resulted in moderate-to-marked improvements.[45] There have been no trials of gabapentin monotherapy in acute mania.

The potential role of lamotrigine and/or gabapentin in acute mania will require prospective, controlled, double-blind testing. Furthermore, there have been no comparisons of the effectiveness of any of the anticonvulsants in acute mania published to date. Hence, statements of the efficacy of one agent over another cannot be made at this time. If there is poor response to valproate, combination treatment, i.e., carbamazepine or lithium along with valproate, should be attempted.[4,46]

Mixed Mania

Valproate is considered a first-line treatment for mixed mania. If ineffective, alternative treatments can include lithium, carbamazepine, or combinations of lithium and valproate.[4,46] No studies examining the potential antimanic effects of gabapentin or lamotrigine have been con-

ducted in mixed manic states as yet. As can be seen in Table 1, patients whose manic symptoms fail to respond to lithium or valproate may be treated with the alternate medication (valproate in the case of lithium nonresponse or vice versa), or supplemental agents. Partial responses to lithium or valproate may be best managed by adjunctive treatments, such as with lithium or carbamazepine. Combination therapies are common in the treatment of refractory bipolar disorder. Combinations of lithium and valproate tend to be safe and effective.[47]

Bipolar Depression

Patients may report that the experience of hypomania, and at times, mania, is pleasant. They may not have sufficient insight into the real and potential hazards that arise from behaviors emanating during such episodes. On the other hand, the experience of depressive episodes can be quite overwhelming. If ineffectively treated by lithium or alternative agents, patients may elect to discontinue their mood-stabilizing medications. In part, this decision may be driven by the assumption that such medications are inefficacious; for some patients, noncompliance is known to lead to recurrence of mania, which is perceived as a more pleasant emotional state. Hence, in addition to reducing the potential morbidity associated with mania, treatment must also reduce the pain and potential serious sequelae associated with depression.

There are no controlled studies assessing the efficacy of valproate in acute depression. However, valproate was relatively ineffective in the treatment of unipolar and bipolar depression in 4 open-label studies.[48] When combined, the 4 studies demonstrated that only 58 (30%) of 195 patients responded to valproate use.

Carbamazepine, on the other hand, has been rather effective in treating bipolar depression. The plausibility of carbamazepine-associated antidepressant effects is reasonable considering that carbamazepine possesses a structure similar to that of tricyclic antidepressants.[49] Longitudinal studies, employing an on-off-on design, demonstrated that carbamazepine was effective in reducing the severity of depressive episodes.[50,51] Unfortunately, the sample sizes of the studies limit the generalizability of the results. In some cases, patients did not relapse into depression during the "off" period, i.e., with drug discontinuation, suggesting that mood improvement could not be unequivocally attributed to carbamazepine.[51] An open study also supported that antidepressant efficacy in 17 (63%) of 27 carbamazepine-treated patients who entered remission after treatment. Controlled studies involving carbamazepine are lacking.

Lamotrigine, either as monotherapy or as adjunctive treatment, appears to have antidepressant effects. Case reports and 4 open-label studies suggest the benefit of supplemental lamotrigine in bipolar patients unresponsive or partially responsive to conventional treatment.[36–38,52–55]

A recent multicenter, randomized, double-blind study employing lamotrigine monotherapy in bipolar depression is worth noting.[56] Patients (N = 192) with bipolar depression of at least 8 weeks' duration were randomly assigned to 1 of 3 conditions for a 7-week period: placebo; lamotrigine, 50 mg/day; or lamotrigine, 200 mg/day. Significant reductions in depressive symptoms were noted among lamotrigine-treated patients compared with the placebo-treated patients. Furthermore, a dose-response relationship was suggested by the clinical improvement of patients in the 200-mg/day group compared with those in the 50-mg/day group.

Among patients with bipolar depression treated with adjunctive gabapentin (mean ± SD dose = 1050 ± 640 mg/day) during a 6-week, open-label trial, 53% of patients (8/15) demonstrated a significant, albeit modest, improvement in scores on rating scales assessing depression severity.[57] Another double-blind study employing gabapentin monotherapy in a small sample of bipolar patients revealed that antidepressant effects of gabapentin occurred within the first week of the trial, but rapidly dissipated by the fifth week of treatment.[58]

Of note, lamotrigine reportedly caused depressed patients to develop symptoms of hypomania.[56] However, the rate of induced hypomania did not statistically significantly differ for lamotrigine-treated and placebo-treated patients. This suggests that the hypomania observed may have been part of the natural course of the bipolar affective illness for these patients, rather than an effect of the lamotrigine per se. By contrast, gabapentin was associated with development of hypomania and accelerated cycling in depressed patients.[41,42,44,57,59,60] Caution, therefore, is required if trials of gabapentin are employed in depressed bipolar patients.

In general, when faced with bipolar depression refractory or intolerant to lithium, carbamazepine is a good alternative[4,46] (see Table 1). While further research is required into its efficacy, lamotrigine may also be of benefit to depressed patients, either as an adjunct to existing treatment or as monotherapy. Gabapentin also requires further investigation; its use would have to be closely monitored to avoid precipitation of a manic episode. Data on the utility of gabapentin and lamotrigine were not available at the time treatment guidelines for bipolar disorder[4,46] were published. Both agents were included in Table 1 since they have potential for treatment, particularly in bipolar depression.

Rapid Cycling

Both valproate and carbamazepine demonstrate efficacy in the treatment of patients with rapid-cycling bipolar disorders.[31,61–63] Consequently, valproate and carbamazepine constitute the first- and second-line treatment recommendations for management of patients with rapid cycling.[4,46] The effectiveness of lamotrigine and gabapen-

tin in rapid cycling has yet to be studied in controlled conditions. Preliminary data from case reports and uncontrolled, small, open-label studies suggest lamotrigine's effectiveness among patients with rapid cycling.[36,38,52,54,55,64] A double-blind, crossover trial of gabapentin and lamotrigine monotherapy suggested that patients with rapid cycling responded well to lamotrigine and, to a lesser extent, gabapentin monotherapy.[58] The small sample sizes in these studies limit the generalizability of results obtained with lamotrigine. Patients unresponsive to valproate or carbamazepine monotherapy may benefit from combinations of those treatments with lithium[4,46] (see Table 1).

Prophylaxis of Recurrent Episodes

In addition to the goal of reducing distress associated with acute episodes, pharmacologic interventions are also aimed at preventing future episodes for patients with bipolar disorder. Open-label studies suggest that valproate reduces the frequency and severity of mood episode recurrences in patients with rapid cycling, mixed bipolar, and bipolar II disorders.[48,62,65–67] As noted previously, valproate may be more effective in reducing the frequency of manic episodes as opposed to depressive episodes.[48,68–71] During a 2-year follow-up period, the mean number of episodes of mood disturbances for valproate-treated patients was less than, although not statistically significantly different from, that for lithium-treated patients.[71]

Preliminary data from a large double-blind study comparing placebo, lithium, and valproate prophylaxis over a 1-year span revealed that valproate-treated patients had fewer affective episodes (either manic or depressive) than either placebo- or lithium-treated patients.[72]

Data from several reports indicate that carbamazepine may effectively reduce the frequency and severity of recurrent episodes of bipolar disorder.[35,73–81] Some of these studies involved comparisons of carbamazepine with placebo[76] and lithium.[35,73,75,77,81] While carbamazepine was found to be more effective in the prophylaxis of recurrences than placebo,[76] comparisons with lithium were more difficult to interpret. Overall, no significant differences in efficacy were found between lithium and carbamazepine.[35,73,75,77] Carbamazepine appeared to lose efficacy on long-term follow-up; in other words, relapse rates tended to be higher for carbamazepine-treated patients.[35,73,77]

A recent randomized multicenter comparison of the prophylactic effects of carbamazepine and lithium was conducted in 144 patients with bipolar disorder for a 2.5-year period. Several outcome measures were employed, including recurrence rates, need for hospitalization, need for concomitant medications, and reported rates of adverse effects. While the hospitalization rates for subjects in the 2 groups were comparable, recurrence rates and the rates of required supplemental psychotropics favored the lithium-treated group. In addition, when com-

pared with lithium-treated subjects, significantly more carbamazepine-treated subjects reported adverse effects. In fact, treatment discontinuation due to side effects was higher among the carbamazepine-treated subjects than among lithium-treated subjects. Lithium may be more effective than carbamazepine in prophylaxis of recurrences of bipolar affective disorder and may be better tolerated for the long-term treatment of bipolar disorder.[82]

The prophylactic effects of lamotrigine and gabapentin as monotherapy or adjunctive mood-stabilizing agents have not been assessed as yet.

Consequently, lithium continues to be recommended as the first choice for prophylaxis.[4,46] However, valproate would certainly constitute a reasonable alternative. Again, for patients with a history of rapid cycling, valproate may be a better option.

ISSUES IN ANTICONVULSANT USE

Primary care physicians caring for a patient with bipolar disorder will need to maintain close contact with the psychiatrist managing medications for bipolar disorder. The primary care physician will need to be aware of the safety and toxicity issues, side effect profiles, and drug interactions associated with anticonvulsant use. These will be described briefly below.

Valproate

Valproate is available in 4 formulations from Abbott Laboratories: valproic acid, divalproex sodium, divalproex sprinkle capsules, and sodium valproate syrup. Valproate is generally begun at 750 mg/day in divided doses. The dose is increased every 2 to 3 days as tolerated to a maximum dose of 1000 to 2000 mg/day. Valproate should be dosed to clinical responsiveness as well as patient tolerance of side effects. Although no definite therapeutic serum level has been established for the use of valproate, levels of more than 50 μg/mL may be associated with a better response in acute mania.[67] The target ranges appear to be 50 to 125 μg/mL.

For hospitalized patients, oral loading of valproate may be particularly worthwhile. Doses are initiated at 20 mg/kg/day and increased as tolerated for clinical responsiveness. Doses are not to exceed 60 mg/kg/day. Oral loading of valproate is safe, rapidly achieves symptom remission,[83] and reduces hospital length of stay.[84,85] Oral loading may not be possible in the elderly and those with comorbid medical conditions, e.g., severe hepatic disease.

The side effects associated with valproate use are summarized in Table 2. Gastrointestinal disturbances are most common. Nausea may be reduced with the use of the sustained-release formulations, such as divalproex sodium.[86,87] However, there is a greater risk of diarrhea with the sustained-release formulations. Tremor develops in approximately 10% of valproate-treated patients, but can

Table 2. Side Effects Associated With Anticonvulsants Used in Bipolar Disorder

Valproic acid
  Nausea, indigestion
  Vomiting, diarrhea, abdominal pain
  Sedation
  Weight gain
  Tremor
  Hair loss
  Poor appetite
  Rash
  Dizziness, confusion
  Thrombocytopenia
  Hepatotoxicity
  Pancreatitis
Carbamazepine
  Sedation
  Nystagmus, diplopia, ataxia
  Nausea, vomiting, diarrhea
  Myoclonus
  Elevated liver enzymes
  Hyponatremia, inappropriate secretion of antidiuretic hormone
  Rash
  Leukopenia, neutropenia
  Aplastic anemia
Lamotrigine
  Dizziness
  Ataxia, diplopia, blurred vision
  Sedation
  Headache
  Vomiting
  Rash, Stevens-Johnson syndrome
Gabapentin
  Sedation
  Dizziness
  Ataxia
  Fatigue
  Nystagmus
  Headache
  Tremor
  Diplopia
  Nausea, vomiting

be reduced with low-dose propranolol or amantadine.[88] Valproate functions as a chelating agent, affecting zinc and selenium levels. Patients so affected may experience transient hair loss. Drug discontinuation is unnecessary, since patients can be treated with selenium and zinc supplements.[89]

Valproate use is also associated with the possibility of elevation of liver enzymes and thrombocytopenia. Transient elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been reported in as many as 11% of valproate-treated patients.[90] However, increases in liver enzymes are generally asymptomatic and usually return to baseline with dose reduction or drug discontinuation. Rare cases of fatal hepatotoxicity have been reported. Similarly, thrombocytopenia has been reported (see Table 2). Thrombocytopenia and hepatotoxicity are rare occurrences early in treatment with valproate. The risk of fatal hepatotoxicity appears to be highest in very young patients, i.e., patients under age 2 years, and declines with age.[91] Furthermore, rates of valproate-associated hepatic toxicity increases in patients receiving

multiple anticonvulsant medications. Significantly reduced platelet counts or evidence of bleeding and excessive bruising during the course of valproate treatment would warrant drug discontinuation.

Valproate has also been implicated in producing variable and, at times, conflicting changes in thyroid indices[92–95]; however, these do not appear to be clinically significant. Very rarely, pancreatic inflammation has been reported with valproate use, usually in younger patients and generally early in the course of treatment.[96] Patients should be informed to contact their physicians if any of the following symptoms occur: unusual bleeding and bruising, right upper quadrant abdominal pain/tenderness, jaundice, darkening of the urine, stools that appear pale, fever, severe confusion, double vision, or severe trembling. The latter 3 symptoms usually signal valproate toxicity and warrant evaluation of serum valproate levels.

The half-life of valproate is 9 to 16 hours. Monitoring serum valproate concentrations is recommended approximately 2 to 3 days after drug initiation or dose increase. The serum level should be obtained in the morning, before the first scheduled dose of the day, to avoid obtaining falsely elevated serum levels. Ideally, to avoid toxicity, serum valproate levels should not exceed 125 μg/mL. In addition to assessing for toxicity, monitoring of serum levels may be helpful when drug-drug interactions that increase valproate levels are suspected or to determine patient compliance. Otherwise, it has been argued that measuring plasma concentrations is of little value if patients are otherwise clinically well controlled.

Because the risk of hepatotoxicity is highest early in the course of treatment, liver function tests should be conducted at monthly intervals during the first 6 months of treatment, and less frequently thereafter.[97] Routine monitoring of pancreatic enzymes is generally not required unless prompted by symptoms of pancreatic inflammation, e.g., epigastric abdominal pain, vomiting, and anorexia. Similarly, routine thyroid function testing is generally not required.

Women of reproductive age should be asked if there are any pregnancies planned, and if so, alternatives to valproate should be explored. There is an increased risk of neural tube defects[98–101] and midline organ malformations[102,103] associated with valproate use, particularly in the first trimester (Table 3). Valproate is also secreted in breast milk during lactation, but its effects on the developing infant are unknown.

Pertinent drug interactions associated with valproate use are listed in Table 4. Valproate tends to inhibit drug oxidation, thereby increasing concentrations of a number of potentially coadministered medications. Medications that displace valproate from protein binding, such as salicylates, can increase valproate levels. Similarly, agents that enhance drug metabolism, such as carbamazepine, can reduce valproate levels.

Carbamazepine

Carbamazepine is employed in doses of 10 to 20 mg/kg/day. The initial dose may need to be lower, e.g., 3 to 5 mg/kg/day, and increased slowly every 5 to 7 days until the desired clinical effect is achieved or until limited by side effects. This approach will determine the lowest effective dose or maximal tolerated dose.

The dose can be administered in conventional tablets or liquid suspension. The total daily dose should be administered in 3 to 4 divided doses to avoid large fluctuations in serum levels. However, in cases where repeated doses produce sedation or interfere with compliance, the doses can be administered twice a day. Slow-release preparations can be used as well.

The side effects associated with carbamazepine use are summarized in Table 2. Neurologic symptoms, such as diplopia, nystagmus, confusion, and ataxia, are dose related and remit with dose reductions. Less common untoward effects associated with carbamazepine use include elevations in the liver enzymes (5%–15% of patients), hyponatremia (6%–31%), and rash (10%–12%).[49] Leukopenia usually occurs early in the course of treatment. Often the white blood cell counts return to baseline without carbamazepine dose modifications.[104–106] Rarely, severe leukopenia, i.e., white blood cell counts below 3000/mm^3 or neutrophils below 1500/mm^3, has occurred, requiring drug discontinuation.[107] Few cases of thrombocytopenia[108] and rare cases of aplastic anemia[104] were reported.

Carbamazepine-associated rash can be treated with steroids. It rarely leads to bleeding or extensive exfoliation, such as in Stevens-Johnson syndrome. Severe hyponatremia has been associated with carbamazepine use, associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[109,110] The mechanisms for carbamazepine-associated SIADH are unclear. Patients may experience severe headache, fatigue, vertigo, and confusion associated with the hyponatremia. Remediation may arise with fluid restriction, carbamazepine discontinuation, and, if necessary, demeclocycline administration.[109,111] Hyponatremia is apt to occur in adults, especially elderly patients. Patients should be apprised of the need to notify their physicians if dermatologic, hepatic, infectious, or hematologic (i.e., bruising and bleeding) symptoms develop. Routine follow-up with patients is required. Routine laboratory examinations may be helpful, but cannot anticipate whether potentially fatal idiosyncratic reactions will occur.

Carbamazepine is implicated in producing reductions in free thyroxine and total thyroxine serum levels as well as serum triiodothyronine levels.[92,93,95] However, clinically significant hypothyroidism has only rarely been reported.[112]

Unlike the therapeutic serum levels found with lithium and valproate, there does not appear to be such a serum level of carbamazepine for acute mania. Previous researchers have reported that acutely manic patients who

Table 3. Safety of Anticonvulsants Used in Bipolar Disorder in Pregnancy and Lactation[a]

Variable	Valproic Acid	Carbamazepine	Lamotrigine	Gabapentin
FDA pregnancy category[b]	D	C	C	C
Teratogenic effects	Neural tube defects, spina bifida Craniofacial defects Cardiac defects Urogenital midline defects Skeletal muscle defects	Neural tube defects, spina bifida Congenital hip dislocation Hypospadia Craniofacial defects Cardiac defects Fingernail hypoplasia Developmental delays	Intrauterine growth retardation Delayed bone ossification	Intrauterine growth retardation Delayed bone ossification
Effects in lactation (breast milk concentration[c])	10%	60%	25%	Unknown

[a]Abbreviation: FDA = U.S. Food and Drug Administration.
[b]C = adverse fetal effects noted in animal studies but no human data available; D = adverse fetal effects noted in humans.
[c]Expressed as percentage of maternal serum drug concentration. Data from reference 121.

Table 4. Drug Interactions Associated With Anticonvulsants Used in Bipolar Disorder[a]

	Drugs Influencing Anticonvulsant Effect		Drug Effects Influenced by Anticonvulsants	
Anticonvulsant	Increase	Decrease	Increase	Decrease
Valproic acid	Amitriptyline Aspirin/salicylates Chlorpromazine Cimetidine Felbamate Fluoxetine/SSRIs Naproxen	Carbamazepine Lamotrigine Phenytoin	Carbamazepine Ethosuximide Lamotrigine Phenobarbital Phenytoin SSRIs Thiopental Tricyclic anti-depressants Zidovudine	Diazepam
Carbamazepine	Acetazolamide Erythromycin Isoniazid Propoxyphene Valproate Verapamil, diltiazem		Antipsychotic medications Benzodiazepines Oral contraceptives Steroids Tricyclic antidepressants Valproate Warfarin	
Lamotrigine	Valproic acid	Carbamazepine Phenytoin		Clonazepam
Gabapentin	Cimetidine	Antacids (eg, Maalox)	Phenytoin	

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.

responded to carbamazepine had serum levels between 4 and 15 µg/mL.[50,113]

Because leukopenia tends to occur early in the course of treatment, periodic monitoring of complete blood counts should be undertaken. Granulocyte counts are warranted in patients presenting with fever and signs of infection. Routine monitoring of liver enzymes is generally not required unless prompted by signs or symptoms of hepatic inflammation, e.g., right upper quadrant abdominal pain, vomiting, anorexia, jaundice, darkened urine, pale colored stools. Routine thyroid function testing is generally not required.

Monitoring of serum drug concentrations can be helpful in evaluating patient compliance or concentration-dependent toxicity. Because of the half-life of carbamazepine, serum carbamazepine concentrations take 3 to 7 days to stabilize. Serum levels should be obtained in the morning, prior to the first daily drug administration for that day.

It is important to remember that carbamazepine activates the hepatic cytochrome P450 enzyme system, inducing those same enzymes that are responsible for its metabolism. Consequently, serum carbamazepine levels may dramatically decrease after a period of time. Hence, the dosage of the carbamazepine taken daily may need to be increased to return to previously effective serum levels at which the patient had been doing well. Such autoinduction of the P450 isoenzymes is likely to occur early in treatment.[114]

Carbamazepine treatment during pregnancy is associated with a number of potential fetal malformations,[115–117] as can be seen in Table 3. The risk of neural tube defects may be reduced during pregnancy with folic acid supplementation in doses of 1 to 4 mg/day in the 4 weeks prior to conception if the pregnancy is planned and throughout the first trimester.[103,118] Carbamazepine is also secreted in breast milk,[119–121] but the long-term effects on the newborn are unknown. Breastfeeding should not be discouraged unless the newborn demonstrates side effects or signs of toxicity associated with carbamazepine.[122]

Multiple drug interactions are possible with carbamazepine[123,124]; several of these are summarized in Table 4. Women, particularly those who wish to avoid pregnancy during carbamazepine treatment, must be apprised of the increased risk of oral contraceptive failures attributed to concomitant carbamazepine use.[103,113] Additionally, while not listed in the table, combinations of carbamazepine with other mood-stabilizing agents may be associated

with the possibility of enhanced neurotoxicity.[125] There may be an increased risk of cognitive deficits associated with combinations of carbamazepine and lithium.[126] The risk of agranulocytosis may be increased if carbamazepine is coadministered with medications potentially producing comparable effects, such as clozapine.

Lamotrigine

Lamotrigine is initiated at 25 mg/day and increased by an additional 25 mg every 2 weeks until the target dose, i.e., 200 to 500 mg/day, is achieved or until side effects preclude further dose increases. Due to the risk of dermatologic side effects, such as rash, the manufacturer cautions against more rapid dose escalations. If the patient is concurrently treated with valproate, the aforementioned dosing regimen is halved.[38] Dose reductions (and corresponding slower dosing increments) are warranted in patients with significant hepatic or renal impairments.

Common adverse reactions associated with lamotrigine are summarized in Table 2. A macular-papular or erythematous rash developed in approximately 10% of 3501 individuals receiving lamotrigine in epilepsy trials.[127–129] Drug discontinuation due to the rash was warranted only in 3.8% of patients, while the rash resolved in the remaining patients despite continued lamotrigine treatment.[127–129] For unknown reasons, the incidence of rash and subsequent drug discontinuation due to the rash has been higher in trials of patients with bipolar disorder.[38,56] Life-threatening rashes, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, occur in 1/1000 treated adults. Patients should contact their physicians if a rash develops during lamotrigine treatment. Rash occurrence is highest in the first 4 to 6 weeks of lamotrigine treatment. In addition, children appear to be particularly vulnerable to rash development; the risk of developing a life-threatening rash is approximated to be 1/50 to 1/100. Lamotrigine should be avoided in young patients, aged 16 years or less. Other factors associated with rash development include coadministration of lamotrigine and valproate, exceeding the recommended initial dose of lamotrigine, or overly aggressive lamotrigine dose escalation.

Animal studies reveal few teratogenic effects.[102] Safe use in pregnancy has not yet been established, but may offer some advantages over valproate and carbamazepine.[130] Because lamotrigine passes into breast milk, nursing while treated with lamotrigine is not recommended (Table 3).

There are a limited number of side effects associated with lamotrigine use, summarized in Table 4. Coadministration of lamotrigine with valproate is associated with an increased risk of life-threatening rash.

Gabapentin

Gabapentin is dosed flexibly with a starting dose of 300 mg b.i.d. The dose can be increased gradually up to a maximal dose of 3600 mg/day. It should be administered in divided doses due to its short half-life (5–9 hours) to maintain adequate serum levels.[131]

Gabapentin has no known potentially fatal effects and few side effects (Table 2). Gabapentin is excreted unchanged from the kidneys; plasma clearance is proportional to the creatinine clearance.[131,132] Dose reductions are required for patients who have compromised renal functioning or require dialysis.[133–135] Fetal risks associated with gabapentin use in pregnancy and lactation are as yet unknown (Table 4), nor has the safety of use in children under the age of 12 years been established.

Gabapentin circulates unbound to plasma proteins and is not appreciably metabolized.[136] Hence, there are no problems arising from coadministration with highly protein-bound medications and virtually no effect on the hepatic cytochrome P450 system, and therefore, there are minimal drug interactions associated with gabapentin[131,132,137] (Table 3). Possible drug interactions between phenytoin and gabapentin have been reported.[138,139]

OTHER ANTICONVULSANTS WITH POTENTIAL FOR USE IN BIPOLAR DISORDER

Increasing attention may be directed at topiramate and other relatively new anticonvulsants, vigabatrin and tigabine, for use in bipolar disorder. The efficacy and safety of these agents in bipolar patients are yet unknown. A preliminary study of the effect of topiramate in 11 acutely manic patients (dose range, 50–1300 mg/day) demonstrated moderate-to-marked improvements in 5 patients (45%).[140] Further study is required to assess the utility of these medications in bipolar patients.

SUMMARY

While lithium carbonate had been the mainstay of treatment, there is increasing evidence for the role of anticonvulsants in the treatment of syndromal variants of bipolar disorder. Valproate is the only anticonvulsant thus far approved by the FDA for treatment of acute mania. It is considered the first-line treatment for mixed mania and rapid cycling, as well as a good alternative for lithium failure or intolerance in the treatment of mania. It appears to be efficacious in the long-term maintenance treatment of bipolar disorder, although not as yet officially FDA approved for this indication. Carbamazepine is a good alternative to valproate in the treatment of rapid cycling and to lithium in the treatment of bipolar depression. Both valproate and carbamazepine are associated with a number of adverse effects and potential drug interactions that necessitate careful patient follow-up and periodic laboratory investigations.

The roles of lamotrigine and gabapentin in the treatment of bipolar disorder (either as monotherapy or as

supplemental agents) have as yet to be clarified. Lamotrigine may be of particular benefit in bipolar depression. It is associated with few drug interactions and may be safer than valproate or carbamazepine in pregnancy. The data, thus far, on the efficacy of gabapentin in bipolar disorder are limited, but warrant further investigation. Gabapentin is safe in patients with significant hepatic disease or who sustain hepatic complications associated with use of valproate or carbamazepine. The lack of significant drug interactions make it safe in patients requiring multiple psychotropic medications. It has virtually no impact on protein-bound medications and does not effect the cytochrome P450 system.

Despite the advances in pharmacologic management of bipolar disorder, it remains a chronic disease with frequent recurrences and exacerbations. Uncontrolled, this disorder can have profound and enduring effects. Pharmacologic treatments that can offset phases of the illness or the recurrent cycles are desperately needed. Future research will assess the utility and safety associated with newer anticonvulsants as well. Familiarity with the expanding treatment options available in bipolar disorder will render the primary care physician effective, working alone or in collaboration with a psychiatrist, in addressing management issues, adverse medication effects, and the potential for drug interactions.

Drug names: amantadine (Symmetrel and others), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), cimetidine (Tagamet and others), clonazepam (Klonopin and others), clozapine (Clozaril), demeclocycline (Declomycin), diazepam (Valium and others), diltiazem (Cardizem and others), divalproex sodium (Depakote), ethosuximide (Zarontin), felbamate (Felbatol), fluoxetine (Prozac), gabapentin (Neurontin), isoniazid (Rifamate and others), lamotrigine (Lamictal), lithium (Eskalith and others), naproxen (Naprosyn and others), phenytoin (Dilantin and others), propoxyphene (Darvocet and others), propranolol (Inderal and others), topiramate (Topamax), valproic acid (Depakene), verapamil (Calan and others), warfarin (Coumadin), zidovudine (Retrovir).

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