# Background and rationale for use of anticonvulsants in psychiatry

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Many individuals with psychiatric illnesses do not respond optimally or are intolerant to conventional treatments. These challenges, and the seriousness and debilitating nature of psychiatric disorders, have stimulated an interest in alternative medications. Studies show a direct correlation between anxiolytic and anticonvulsant properties, and the link between epilepsy and psychiatric disorders has been clinically recognized for many years. Alternative uses for anticonvulsants have been well documented, and our understanding of the clinical spectrum of these agents has advanced significantly in recent years. The emergence of novel anticonvulsants with improved pharmacokinetics has led to investigations of their use in bipolar disorder, pain syndromes, obsessive compulsive disorder, panic disorder, social phobia, Alzheimer's disease, behavioral disturbances, anxiety, insomnia, depression, posttraumatic stress disorder, and drug withdrawal. The effectiveness of standard treatments for bipolar disorder and prospects for alternative medications are discussed.

## HISTORY OF THE USE OF ANTICONVULSANTS IN PSYCHIATRY

Except for phenytoin, early anticonvulsants, such as bromides and phenobarbital, were primarily sedatives and anxiolytics. After the introduction of benzodiazepines in the 1960s, anticonvulsants evolved into a class of drugs distinct from psychiatric drugs used to control behavior and anxiety. Some conventional anticonvulsants still widely used today were approved originally for psychiatric use or have been used extensively for indications outside the approved labeling of the US Food and Drug Administration (FDA).

In the late 1950s, coincident with the discovery of the anticonvulsant properties of carbamazepine, Blom[1] and Bonduelle et al[2] demonstrated the beneficial effect of carbamazepine in trigeminal neuralgia. Trigeminal neuralgia remained the only approved indication for carbamazepine for many years in the United States.[3] Subsequently, carbamazepine was reported to have beneficial effects in affective disorders.[4,5] In the 1970s, carbamazepine became the first anticonvulsant used for bipolar disorder.[6]

Although valproate is considered primarily an anticonvulsant, its use in primary psychiatric disorders dates back to 1966. The role of γ-aminobutyric acid (GABA) in mood provided the basis for investigations of valproate in this setting,[7] and valproate is now also approved for the treatment of migraine and bipolar disorder.

In the 1970s, investigation of clonazepam for mania was based on its known anticonvulsive properties[8] and on the antimanic properties of valproate and carbamazepine.[9–11] The use of clonazepam was precipitated by the need for supplemental or alternative treatments to lithium. Neuroleptic agents were being used, but disabling side effects emerged as an obstacle to their acceptance.[12] Clonazepam is widely used in bipolar and anxiety disorders but is currently approved only for epilepsy.

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Preliminary investigations of the use of newer anticonvulsants in psychiatry were based largely on the success of conventional antiepileptic drugs. Research now supports the efficacy of newer agents, such as gabapentin, lamotrigine, and topiramate, for bipolar disorder. The positive clinical response of psychiatric disorders to anticonvulsants has prompted discussion of possible links between seizure disorders and psychiatric illnesses.

## EPILEPSY, BIPOLAR DISORDERS, AND PAIN

### Symptoms, pathology, and drug response

Numerous theories have been offered to explain the commonality of epilepsy, bipolar disorder, and pain. Psychiatric disorders often coexist with or complicate the management of patients with epilepsy[13]; up to 50% experience psychotic symptoms or mood disorders. It is not known whether these symptoms arise from psychosocial issues or from deviations in neurochemistry, electrophysiology, or medication effects.[13]

Any examination of similarities between these disorders must acknowledge that anticonvulsants have achieved a similar positive response in epilepsy and psychiatry. Similar changes in temporal lobes of persons with bipolar disorder and those with epilepsy have also been reported, providing a possible explanation for the positive response of bipolar disorder to anticonvulsants.

## PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

### Approved medications

The diversity of manifestations of bipolar disorder presents a major clinical challenge.[6] Symptoms can fluctuate from one episode to the next, and recurrences of mania and depression are common.[6] Clinicians must differentiate among classic manias, euphoric manias (bipolar I), hypomanias with episodes of depression (bipolar II), mixed episodes, or rapid cycling.[6] Because monotherapy is frequently ineffective in bipolar disorder,[6] multiple drug regimens have become more of a consideration, increasing the likelihood of drug interactions and noncompliance. In the United States, lithium and valproate are the only drugs approved for bipolar disorder.

**Lithium.** The antimanic properties of lithium were recognized by John Cade in 1949. Lithium became the treatment of choice for bipolar disorder in Europe in the 1950s and 1960s, and superceded chlorpromazine in the United States in the 1960s.[6] Numerous controlled studies have established the efficacy of lithium for both acute and maintenance treatment.[14,15] Lithium remains the only drug shown to be advantageous for maintenance treatment of bipolar disorder and appears to be more effective as a single agent than any other drug class. However, lithium is effective in only 40% to 50% of patients,[16] and many people are unable to tolerate it because of numerous side effects, including nausea, vomiting, dyspepsia, diarrhea, hair loss, acne, tremor, sedation, decreased cognition, and impaired coordination.[17] Lithium has a narrow therapeutic window, and laboratory monitoring is necessary. Increasing the dosage by even a few pills a day or losing fluid through perspiration can change therapeutic levels to toxic levels. There are also long-term renal and thyroid effects. The overall limited benefits of lithium have been well recognized, especially for rapid cycling or mixed episodes.[6]

**Valproate.** Valproate has been approved by the FDA for acute bipolar disorder, and its use has increased significantly in recent years.[18] Although many patients receive valproate for maintenance treatment, its efficacy for long-term use has not yet been established. The addition of valproate to lithium is considered a first-line treatment for mania refractory to lithium monotherapy.[6] The combination of valproate and lithium is most effective in patients with rapid cycling or mixed episodes.[6] The possibility of oral loading with valproate makes it valuable for achieving rapid stabilization in manic patients.

Valproate, however, is associated with severe side effects. Patients need to be educated about the signs and symptoms of hematologic, pancreatic, and hepatic dysfunction and warned about the potential for hair loss, appetite stimulation, and weight gain before starting treatment.[7] Valproate also is associated with neural tube defects in the developing fetus; thus, there are major concerns about its use in women of childbearing age, particularly since at least half of pregnancies are unplanned.[19]

Menstrual disturbances, polycystic ovaries, and hyperandrogenism may be associated with valproate therapy.[20,21] Reproductive disorders are more common in women with epilepsy than in normal women; these have been attributed to epilepsy itself, but may be related to antiepileptic drug ther-

apy.[20] Isojarvi et al[20] studied 238 women with epilepsy to assess the possible association of polycystic ovaries and hyperandrogenism with valproate therapy. Among 31 women receiving valproate alone or with carbamazepine, 21 (68%) had polycystic ovaries or high serum testosterone levels, compared with 22% of women receiving carbamazepine alone and 18% of controls (*Figure 1*).[20] Among women receiving valproate alone, 13 (45%) had menstrual disturbances compared with 120 (19%) of women receiving carbamazepine ($P = .004$).[20]

Polycystic ovaries or elevated serum testosterone levels were more common in women who started taking valproate or other medications in adolescence; 80% of women treated with valproate before age 20 years compared with 27% of women treated with other antiepileptic drugs had these conditions ($P = .002$).[20] For women treated at 20 years or later, 56% treated with valproate compared with 20% treated with other drugs had these conditions ($P = .004$).[20] The features characterizing the endocrine disorders in women with epilepsy treated with valproate, particularly those starting treatment as adolescents,[20] are like those characterizing full-blown polycystic ovary syndrome.[22] These findings raise concerns about the use of valproate in young women.

A subsequent investigation by Isojarvi et al evaluated the risks associated with hyperinsulinemia in 16 women with valproate-related polycystic ovaries or hyperandrogenism and assessed the reversibility of these conditions.[21] Substitution of lamotrigine for valproate resulted in a decrease in the total number of polycystic ovaries from 20 to 11 and in improvement in insulin and testosterone levels and cholesterol ratios in the 12 women who completed the 12-month follow-up.[21] These risks suggest that alternative treatments should be considered in patients who gain weight during valproate treatment, especially young women with epilepsy.[21]

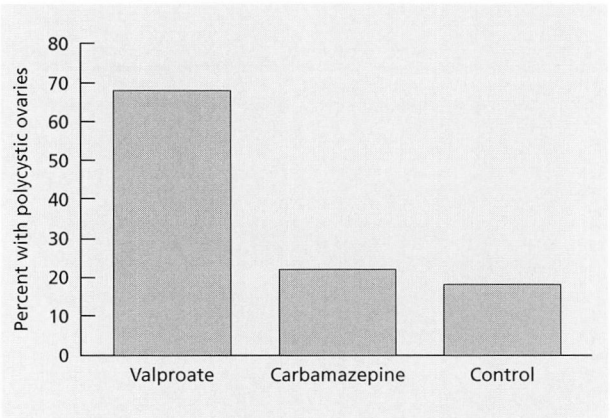


**FIGURE 1. Polycystic ovaries in women taking valproate for epilepsy. Adapted from Isojarvi JIT et al. N Engl J Med 1993; 329:1383–1388.**

## Conventional alternative treatments

**Carbamazepine.** Carbamazepine was the first anticonvulsant used for bipolar disorder.[6] More than 14 double-blind, controlled studies, including a total of approximately 300 patients, have demonstrated superiority of carbamazepine over placebo or its approximate equivalence to lithium for acute mania.[17] The average response rate was 55% to 70%.[23,24] However, use of carbamazepine for bipolar disorder is decreasing because of side effects and increased use of valproate.[6]

**Clonazepam.** Clonazepam was cited as a potential antimanic agent because of its anticonvulsant properties.[8] Generally used as add-on therapy, clonazepam has shown efficacy and tolerability in controlled studies, although it has not been studied as well as valproate or carbamazepine for bipolar disorder. Sedation, cognitive and psychomotor impairment, and potential for abuse are potential drawbacks to its use. Clonazepam is used to treat insomnia and agitation in patients with acute mania, which may represent sedative, rather than antimanic, effects.[17]

## Novel alternative medications

The limitations of approved medications and the potential efficacy of anticonvulsants other than valproate and carbamazepine in bipolar disorder initiated investigations of several newer antiepileptic drugs, such as lamotrigine, gabapentin, and topiramate, whose pharmacokinetic profiles make them safer to use in multiple drug regimens.

**Lamotrigine.** Lamotrigine is indicated as adjunctive treatment for partial seizures. Its probable mechanism of action, inhibition of release of excitatory amino acids such as glutamate, could account for potential mood stabilization properties.[25] More than 200 case studies have been used to evaluate lamotrigine as a mood stabilizer in patients with schizoaffective or bipolar disorders.

Up to 82% of patients with rapid cycling bipolar disorder do not respond adequately to lithium, which has poor-to-moderate antidepressant proper-

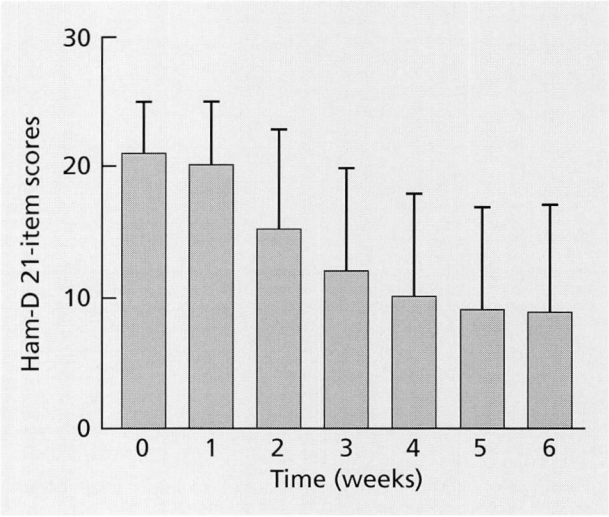


**FIGURE 2. Mean (± SD) Hamilton Rating Scale (21-item) scores at weeks 0–6 in bipolar depressed patients. Patients had been on valproate monotherapy for 2 weeks and lamotrigine was added at week 0. Reprinted with permission from Kusumakar V and Yatham LN. Psychiatry Res 1997;72:145–148.**

ties.[26] Calabrese et al recently suggested that lamotrigine might be effective for the depressed phase of bipolar rapid cycling.[26] A patient in the depressed phase of rapid cyling bipolar I disorder who had been unresponsive to lithium, fluoxetine, and carbamazepine was treated with lamotrigine monotherapy (started at 25 mg/day; titrated to 200 mg/day).[26] The patient's depression improved (Hamilton Depression Rating Scale [HAM-D] declined from 46 at baseline to 9 at 20 weeks). Side effects included fatigue and swelling of lower extremities. During an 11-month follow-up, the patient remained euthymic without rapid cycling, suggesting that lamotrigine may complement lithium and other anticonvulsants in bipolar disorder.[26]

Kusumakar and Yatham treated seven patients with rapid cycling bipolar disorder (six newly diagnosed) with lamotrigine (dosage, 100–500 mg/day).[27] Four of the six newly diagnosed patients responded to lamotrigine within 3 weeks and continued to do well. The two unresponsive patients continued to have depressive or mixed episodes. In the patient with chronic rapid cycling bipolar disorder, valproate controlled hypomania but not depressive episodes; lamotrigine was added to valproate during a depressive episode and these symptoms remitted.[27]

Kusumakar and Yatham added lamotrigine to lithium treatment in 22 patients with bipolar depression refractory to standard treatment.[28] Improvement (≥ 50% reduction in HAM-D score) started during week 1 and continued throughout the study (6 weeks); 16 (72%) of the 22 patients responded by the end of 4 weeks. By week 6, 14 (63%) patients were in remission (HAM-D score ≤ 6) (see *Figure 2*).[28] All patients tolerated the medications well, and none developed rash.[28]

Sporn and Sachs evaluated lamotrigine (dosage, 50–250 mg/day) in 16 patients with refractory bipolar type I or II disorder.[25] Eight were considered responders (mean 5 weeks after initiation of lamotrigine).

These reports suggest that lamotrigine has broad efficacy and tolerability and greater efficacy than lithium and valproate in depressive episodes. However, confirmatory controlled studies are necessary. Because approximately 10% of patients treated with lamotrigine develop rash, which in rare cases can lead to Stevens-Johnson syndrome or toxic epidermonecrolysis,[29] patients should be monitored closely. Stevens-Johnson syndrome occurs more frequently in children (1/50) than in adults (1/1000) treated with lamotrigine. Rash is more likely (18%) when lamotrigine is given in combination with valproate.[29]

**Gabapentin.** Gabapentin is a novel anticonvulsant indicated for adjunctive treatment of partial and generalized seizures. Gabapentin was synthesized as a γ-aminobutyric acid (GABA) analogue but, in fact, does not modulate GABA receptor function. Its precise mechanism of action remains unknown. It probably interacts with the GABA transporter and increases GABA levels in a dose-related fashion.[30] It has been shown to decrease glutamate levels in the rat brain.[30] It is not metabolized in humans and has no known pharmacokinetic interactions with other anticonvulsants.[30]

The rationale for using gabapentin as a mood stabilizer was quite different from that for lamotrigine. Beneficial effects of gabapentin on mood and quality of life were observed in the original treatment population of patients with epilepsy (see *Figure 3*).[31] There are now more than 200 published case reports of gabapentin use in patients with bipolar and schizoaffective disorders.

The initial report of effects of gabapentin on mood consisted of a 24-month, open-label, follow-up study of 35 patients with epilepsy.[32] Some

patients reported a sense of well-being, with improvements in memory, mood, and perception, when gabapentin was added to standard therapy. However, because these results were not anticipated, the number of patients with this experience was not consistently recorded.

Schaffer and Schaffer first reported the use of gabapentin in patients with refractory bipolar disorder. Of the 28 patients, 10 had bipolar I disorder, 10 had bipolar II disorder, seven had cyclothymic disorder, and one had unspecified-type disorder. None had responded adequately to previous treatment with lithium, valproate, or carbamazepine. Eighteen (64%) responded positively to gabapentin. Among responders, the duration of treatment was 9 months or more for 10 patients, 6 months for six patients, and 1 to 3 months for two patients. The most common side effects were oversedation and overactivation.[33]

McElroy et al[34] cited experience with adjunctive treatment with gabapentin in nine patients with bipolar I or II disorder who had hypomanic, manic, or mixed states unresponsive to mood stabilizers.[34] Seven showed marked improvement in manic symptoms by 1 month, and an additional patient showed moderate improvement by 3 months. Six of these eight patients had antimanic responses for periods ranging from 1 to 7 months. Side effects were mild, transient, and generally neurologic in nature.[34]

In another report, five patients with bipolar I or schizoaffective disorder who received adjunctive therapy with gabapentin responded (three had a marked response; one, a moderate response; and one, a mild response). The marked responses were associated with higher doses (1500 mg, 1800 mg, and 2400 mg/day). The only side effect, sedation, occurred in two patients.

The largest study of gabapentin reported to date for bipolar disorder was a retrospective study of 73 patients (55 adults, 18 adolescents) with bipolar I or II, bipolar not otherwise specified, or schizoaffective disorder who had not responded to or were intolerant of a variety of medications. Therapeutic levels of lithium, carbamazepine, and valproate were maintained unless side effects occurred. The mean daily dosage of gabapentin was 900 to 2400 mg in adolescents and 200 to 3500 mg in adults. Rapid cycling ceased in all patients. Twenty-three patients (six adolescents, 17 adults) reported improved mood. Adults reported improvements in memory and attention (20), energy (15), sleep (17) and libido (5). Overall, 67 of 73 had a positive response to gabapentin, enabling them to resume normal activities.[35]

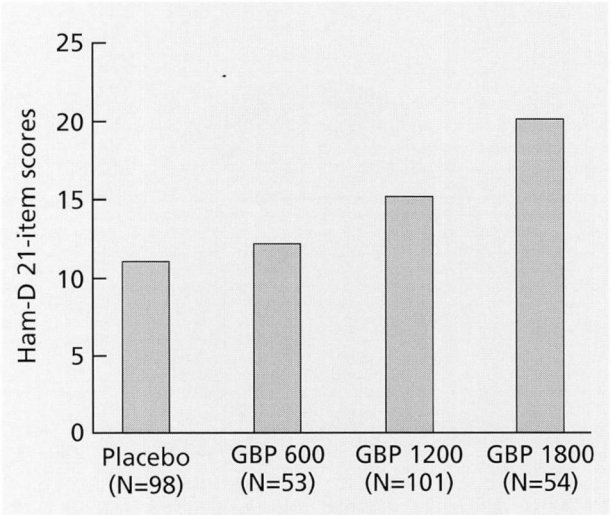


**FIGURE 3. Beneficial effects of gabapentin on quality of life in epilepsy add-on trials. GBP = gabapentin.**

Marcotte conducted a retrospective chart review of patients with bipolar disorder who received gabapentin as adjunctive therapy, evaluating duration of mood-stabilizing effects. After 6 months of treatment, the majority of patients had improved mood, particularly regarding irritability (see *Figures 4* and 5).

Data from randomized, controlled studies are needed to further establish the efficacy of gabapentin as a mood stabilizer. The data presented here indicate that gabapentin holds promise for treatment of bipolar disorder. In addition, it has an excellent safety profile, does not necessitate laboratory testing, and can be titrated easily and rapidly. The absence of protein binding and metabolism limit interactions, making it ideal for combination therapy.

**Pregabalin.** Preliminary evidence suggests that pregabalin, a gabapentin analogue, has anxiolytic, anticonvulsant, and analgesic properties. Extensive clinical trials are planned to evaluate pregabalin in a wide range of neurologic and psychiatric disorders.

**Topiramate.** Topiramate is a sulfamate- substituted monosaccharide indicated for adjunctive treatment of adult partial-onset epilepsy.[36] The pharmacologic properties that may contribute to its effects include a modulatory effect on sodium conduc-

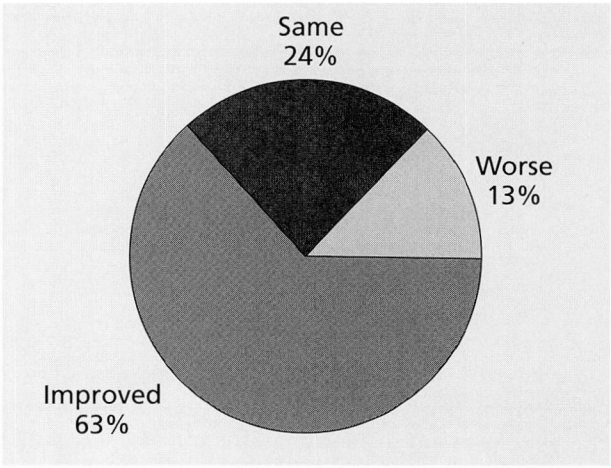


FIGURE 4. Effects of gabapentin on mood in patients with bipolar disorder (N = 38). Adapted from Marcotte (unpublished data).

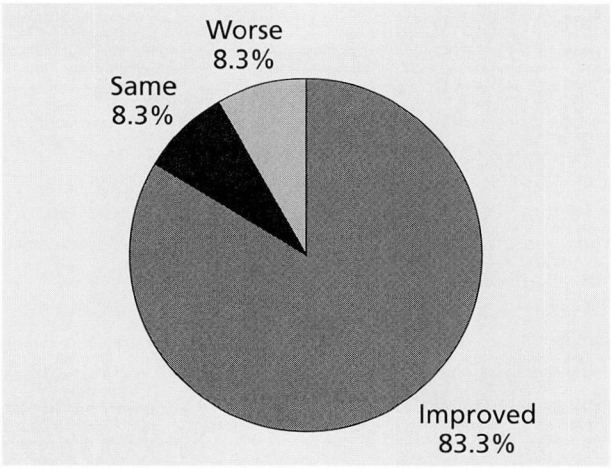


FIGURE 5. Effect of gabapentin on irritability in patients with bipolar disorder (N = 12). Adapted from Marcotte (unpublished data).

tance, enhancement of GABA activity, antagonism of the kainate aminomethyl phosphonic acid subtype of the glutamate receptor, and inhibition of carbonic anhydrase.[36]

Preliminary reports indicate that topiramate may be useful in refractory mood disorders. Marcotte evaluated topiramate (initial dosage, 25 mg bid; mean final dosage, 200 mg/day) as adjunctive therapy in 23 consecutive outpatients with mood disorders (12, bipolar I disorder; 6, bipolar II disorder; 3, cyclothymic disorder; 1, general anxiety disorder; 1, organic psychosis) refractory to other treatments, including anticonvulsants.[37] Thirteen patients (57%) showed marked or moderate improvement; four, minimal or no improvement; and six were rated worse, primarily because of topiramate-related side effects (eg, anxiety, confusion, hallucinations). Other side effects included somnolence, fatigue, and impaired concentration and memory.[37]

Calabrese et al evaluated topiramate for acute management of treatment-refractory mania in patients with bipolar I disorder (initial dosage, 50 mg/day; mean final dosage, 614 mg/day).[38] Three patients demonstrated a > 50% improvement in the mania score, and two showed a 24% to 49% improvement.

The most frequently reported side effects of topiramate are somnolence, dizziness, ataxia, speech disorders, cognitive dysfunction, psychomotor slowing, headache, nausea, nystagmus, tremor, fatigue, gastrointestinal upset, visual disturbances, and renal calculi.[36] Dose-related side effects include mood lability, weight loss, anorexia, tremor, fatigue, nervousness, difficulty concentrating, confusion, depression, and anxiety.[39,40] Because the cognitive effects of topiramate are a concern, controlled studies assessing these factors are needed.[41]

Patients receiving topiramate have a two- to fourfold increased risk of nephrolithiasis. The risk is especially high in patients at risk for kidney stones, such as those receiving other agents increasing risk (eg, acetoazolamide, triamterene and sulfas, antacids, vitamins A and D) and who have disordered parathyroid function.[39,40]

The efficacy, safety, and dosing of topiramate for bipolar disorder remain to be established in further studies.

## OTHER USES OF NEW ANTICONVULSANTS IN PSYCHIATRY: GABAPENTIN

A recent anecdotal report describes the reduction of cocaine craving in an addicted woman taking gabapentin. A 41-year-old woman with posttraumatic stress disorder who had used crack cocaine for at least 1 year and had last used cocaine 3 months before admission revealed that she started taking her husband's gabapentin (600 to 1500 mg daily) when she stopped using cocaine and noticed a decrease in her craving.[42]

The neurobiologic basis of cocaine abuse and dependence is thought to involve transmitter systems that act with the dopamine system in the ventral tegmental area (VTA).[43] Cocaine inhibits GABA release in the VTA,[44] and GABA receptor

function may decrease after repeated cocaine doses.[45] Animal studies suggest that gabapentin may increase GABA turnover in various regions of the brain.[46] Other drug therapies for cocaine abuse have not established clinical efficacy[42]; thus, it is important to follow up this chance finding with further studies.

Gabapentin demonstrated antianxiety and hypnotic effects in psychiatric patients requiring adjunctive anticonvulsant therapy and/or benzodiazepines and who had a primary or comorbid anxiety disorder.[47] Eighteen patients were treated prospectively with gabapentin. Ten had schizophrenia; four, schizoaffective disorder; and three, bipolar disorder. Comorbid conditions included panic disorder (three), alcohol dependency (four), obsessive-compulsiveness (two), and drug dependency (one). One patient had generalized anxiety with comorbid major depression. All but one patient, who continued valproate, had their current anticonvulsant replaced with gabapentin. Anxiety-related symptoms were ameliorated in 14 of the 18 patients (dosage, 200–1800 mg daily); all had improved sleep and reduced anxiety. Two patients discontinued gabapentin because of side effects (interaction with fluoxetine; toxicity due to high doses of gabapentin and valproate). Drowsiness and dizziness at the initiation of therapy were the most common side effects.[47]

In one reported case, gabapentin was successful in treating behavioral dysfunction. A 13-year-old boy with multiple hospital admissions had a history of temper tantrums, screaming fits, violent behavior, mood swings, and depression. Imipramine improved his insomnia; although the frequency of his tantrums decreased, their intensity increased. Other drug therapies, all in combination with imipramine, were ineffective in controlling his behavior. The patient was hospitalized and received gabapentin, 1200 mg/day, over 4 days. Explosive episodes decreased in frequency and intensity. Four months after hospital discharge, his behavior remained well controlled.[48]

## DISCUSSION

The clinical experience with new anticonvulsants is limited; therefore, randomized, well-controlled trials are necessary to firmly establish their roles in psychiatry. The greater cost of these new drugs compared with conventional treatments may be an issue. Since these drugs are used primarily as adjunctive therapy, the addition of a medication may add to compliance problems with the entire regimen. Although the newer agents discussed are generally well tolerated, some side effects, such as the risk for serious rash with lamotrigine or potential dose-related cognitive effects with topiramate, may make psychiatrists reluctant to use them.

Arguments for the use of new anticonvulsive agents are compelling: eg, the problems and failures associated with alternative treatments; the encouraging results from many studies done to date, particularly those for gabapentin; and the improved pharmacokinetic and safety profiles of these agents.

Until comparison studies are done, we will not know the place of either the newer or older agents in the treatment algorithm, regardless of indication, and the relative merits of newer agents as monotherapy versus adjunctive therapy. More specific identification of the patients and disorder subtypes most responsive to these newer agents is necessary. Lastly, research is needed on the benefits and risks of these drugs in the elderly and children, an especially important group since most psychiatric disorders begin early in childhood and adolescence.

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