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NEW TREATMENT STRATEGIES IN PSYCHIATRY: ROLE OF ANTICONVULSANTS

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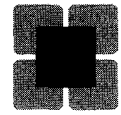

Introduction and overview: The role of anticonvulsants in psychiatry

GEORGE E. TESAR, MD

Anticonvulsant drugs have emerged as effective clinical tools for the treatment of various psychiatric disorders. The links between epilepsy and psychiatry have been well documented. In 1970, Japanese psychiatrists revealed that carbamazepine, considered then for use only in trigeminal neuralgia and epilepsy, had antimanic properties.[1] Since that time, knowledge of the efficacy and limitations of these drugs in psychiatric disorders has increased significantly, and will continue to do so with studies involving four new anticonvulsants—gabapentin, lamotrigine, topiramate, and tiagabine.

The goal of this symposium is to disseminate the information available about the emerging psychiatric uses of anticonvulsant agents and more specifically to provide a better understanding of the pharmacokinetics of the new anticonvulsant agents; to review the underlying rationale of anticonvulsant use in psychiatry in general and specifically in neuropathic pain and withdrawal syndromes; to compare and contrast traditional versus current treatment protocols in bipolar disorders; and to evaluate new strategies for treating panic disorder and social phobia.

Dr. Norman Sussman reviews the historic background and rationale for the use of anticonvulsants in psychiatry. He examines issues concerning the use of the new anticonvulsants, particularly gabapentin and lamotrigine, in psychiatric disorders and reviews the evolution of pharmacologic treatments for bipolar disorder, evaluating the effectiveness of currently approved medications (lithium and valproate) and conventional anticonvulsants (valproate and carbamazepine). Dr. Sussman reviews several clinical studies showing gabapentin and lamotrigine to be effective alternatives for the treatment of bipolar disorder, but cautions that additional studies are needed to determine what specific role these new agents might have in the treatment algorithm.

Dr. Harold Morris reviews the pharmacokinetics of the new anticonvulsants, felbamate, gabapentin, lamotrigine, tiagabine, topiramate, and vigabatrin. The pharmacokinetic profiles of these new anticonvulsants are significantly better than those of the conventional antiepileptic drugs—limited drug interactions make them safer and easier to use. However, with the exception of gabapentin, all these new agents have hepatically mediated drug interactions; thus, more pharmacokinetic studies are required for optimal utilization. Studies to gain insight into their mode of action may reveal new pathways, identify drug interactions, and define adverse effects. This will facilitate the establishment of appropriate treatment guidelines for their use in psychiatry.

Dr. Edward Covington reviews the use of anticonvulsants in neuropathic pain and detoxification. Anticonvulsants have been used in the treatment of neuropathic pain since the early 1940s. However, the conventional agents were generally not effective in this area. The rationale for the use of anticonvulsants in pain is similar to their rationale for use in epilepsy—that is, they suppress discharges in pathologically altered neurons. Neuropathic pain, or abnormal pain, can be best defined as a disproportion between

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the pain signals and the provoking stimulus, if, in fact, a provoking stimulus exists. Dr. Covington examines the pathophysiology of neuropathic pain and the acting mechanisms of conventional and new anticonvulsants in pain. Particular attention is given to studies that demonstrate the superior analgesic effects exhibited by the new anticonvulsants.

In addition, this article discusses the efficacy of anticonvulsants in the treatment of withdrawal symptoms occurring after the discontinuation of sedative-hypnotic drugs and alcohol. Dr. Covington reviews early clinical experiences with carbamazepine and valproate and examines recent studies of gabapentin in sedative-hypnotic withdrawal and alcohol withdrawal.

Without a thorough understanding of pain and drug mechanisms, response predictions for anticonvulsants in the management of neuropathic pain and withdrawal syndromes are limited. It is of interest, however, that the anticonvulsants that are most useful for neuropathic pain are the most effective for sedative-hypnotic withdrawal and bipolar disorder. This raises the question of whether commonality exists in these disorders, and whether neural hypersensitivity and kindling may be an underlying unifying construct.

Dr. Gary Sachs reviews current treatments and new strategies for bipolar disorder. Lithium is considered to be the standard treatment for new onset bipolar disorder. However, many patients are not able to tolerate lithium, and certain subtypes of bipolar disorder are resistant to lithium treatment.[2] Recognition of the overall limited benefits of lithium sparked interest in alternative treatments. Carbamazepine was the first anticonvulsant used for bipolar disorder in the 1970s. Thereafter, valproate became widely used and is the only medication other than lithium to be approved in the United States for treating bipolar disorder.

Emerging evidence indicates that gabapentin, lamotrigine, and topiramate hold considerable promise as adjunctive or alternative treatments in refractory bipolar disorder. This article evaluates the traditional pharmacologic approaches to bipolar disorder and the recent clinical experiences with the new anticonvulsants. The role of practice guidelines in the treatment of bipolar disorder is discussed as well.

Lastly, Dr. Jonathan Davidson reviews the current treatment options and new strategies for panic and social phobia, two areas that offer very little in clinical experience and data concerning treatment with anticonvulsants. Panic disorder is a condition that affects 3.5% of adults in the United States. The phenomenology of panic disorder, including "paroxysmal" onset and short duration of attacks, psychosensory symptoms, dissociative states, and vegetative arousal, resembles that of complex partial seizures, thus creating a strong rationale for the use of anticonvulsants as alternative treatment.

The first part of this article reviews the standard pharmacologic treatment strategies for panic disorder—tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), serotonin-selective reuptake inhibitors (SSRIs), and benzodiazepines—while considering the potential role of valproate and other anticonvulsants.

The second part of this discussion examines the treatment of social phobia, an extraordinarily common disorder. Social phobia is best defined as a pathologic fear of scrutiny by other people in social settings, with a marked and persistent fear of performance situations.

In the past, pharmacologic therapy had not been considered first-line treatment for social phobia due to problems diagnosing and defining this disorder.[3] Now that the two distinct forms of social phobia, discrete or nongeneralized and generalized, are clinically recognizable, treatment can be targeted more specifically to relieve symptoms.[3] Among the anticonvulsants, gabapentin in particular shows considerable promise in treating social phobia. Results of a 14-week, placebo-controlled, double-blind trial evaluating the efficacy and safety of gabapentin in social phobia are analyzed.

Because of their unique mechanisms of action and improved pharmacokinetic profiles, the new anticonvulsants have provided clinicians with increased treatment options for patients with psychiatric disorders. The initiation of randomized, controlled studies is warranted to clearly define the clinical spectrum of these new agents and their position versus conventional therapies. These elements will be critical in determining the direction of future research in psychopharmacology.

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Background and rationale for use of anticonvulsants in psychiatry

NORMAN SUSSMAN, MD

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]

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]

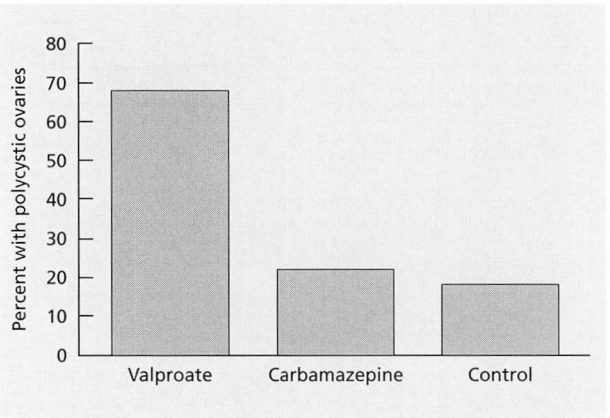

FIGURE 1. Polycystic ovaries in women taking valproate for epilepsy. Adapted from Isojarvi JIT et al. N Engl J Med 1993; 329:1383–1388.

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-

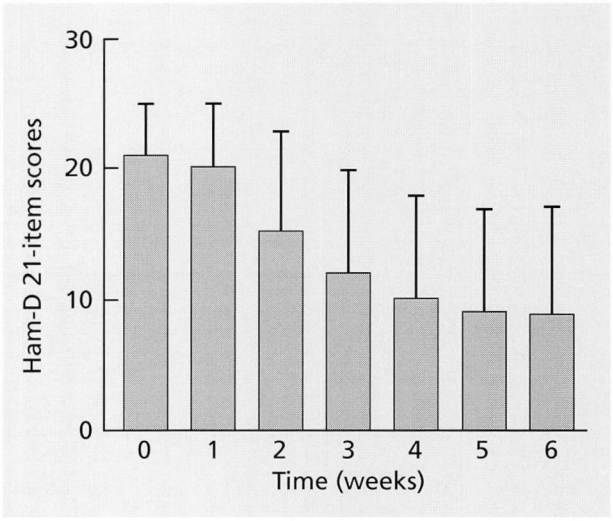

FIGURE 2. Mean (± SD) Hamilton Rating Scale (21-item) scores at weeks 0–6 in bipolar depressed patients. Patients had been on valproate monotherapy for 2 weeks and lamotrigine was added at week 0. Reprinted with permission from Kusumakar V and Yatham LN. Psychiatry Res 1997;72:145–148.

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]

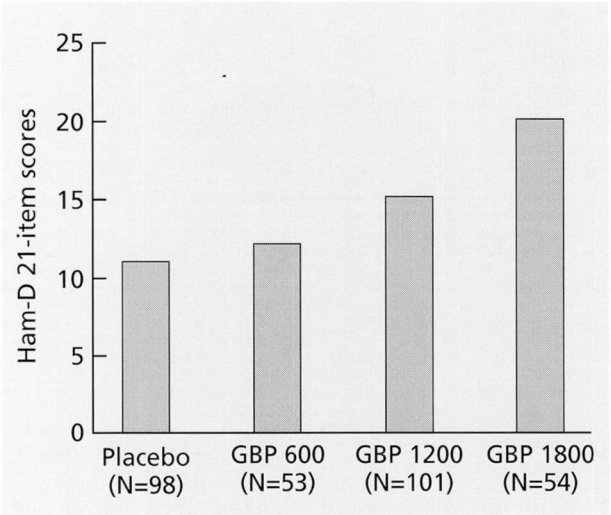

FIGURE 3. Beneficial effects of gabapentin on quality of life in epilepsy add-on trials. GBP = gabapentin.

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-

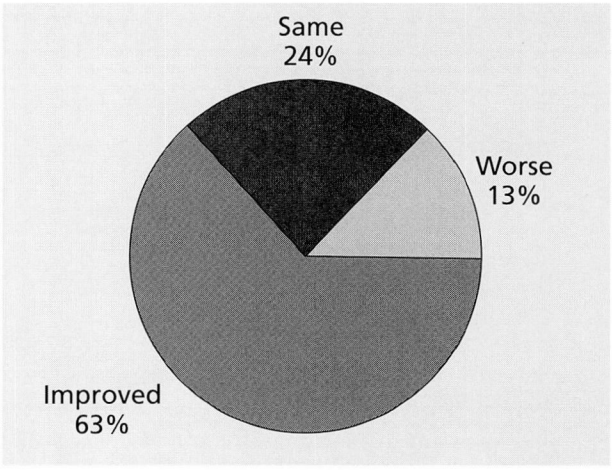

FIGURE 4. Effects of gabapentin on mood in patients with bipolar disorder (N = 38). Adapted from Marcotte (unpublished data).

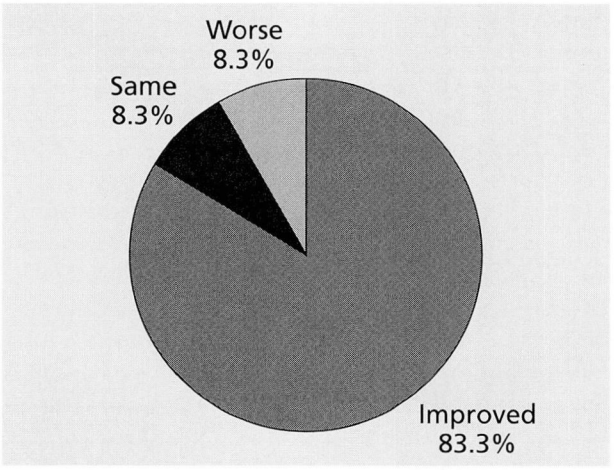

FIGURE 5. Effect of gabapentin on irritability in patients with bipolar disorder (N = 12). Adapted from Marcotte (unpublished data).

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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Pharmacokinetics of new anticonvulsants in psychiatry

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Since bromide was used for catamenial seizures and hysteria by Locock in the mid-1800s, antiepileptic drugs (AEDs) have been utilized in the treatment of various psychiatric disorders.[1] Today, valproate and carbamazepine are important therapies for treatment of mania and bipolar disorder. Now, a number of newer anticonvulsant agents—including gabapentin, lamotrigine, topiramate, and tiagabine—with improved pharmacokinetic profiles are being investigated for psychiatric indications as well. In addition, the range of their psychiatric utility has been expanded, and the effect of AEDs is currently being considered not only in bipolar disorder but in panic and social phobia and in the treatment of neuropathic pain and detoxification.

The mechanisms by which these agents influence mental status and pain perception is unclear, but a review of their pharmacologic properties may reveal some potential mechanisms of action. In addition, an outline of their metabolism, drug interactions, and adverse effects will help to establish their most appropriate administration guidelines and most effective application in the psychiatric arena.

IMPROVING THE PHARMACOLOGIC PROFILE

Several pharmacologic features of the older AEDs have complicated their use. A short half-life necessitating multiple daily doses can undermine patient compliance with several of the agents.[2] High protein binding associated with some of the drugs may also result in drug interactions.[3] In addition, active metabolites of carbamazepine, valproic acid, and primidone alter the safety profile of several compounds; hepatic metabolism and clearance complicate the use of most older AEDs. All of the older AEDs are known to interact with other drugs.

The newer AEDs have an improved pharmacologic profile providing greater anticonvulsant activity while improving patient tolerability and safety. The pharmacokinetic properties of the ideal AED have been described by Gram (*Table 1*).[4] Do the newer available anticonvulsant agents used in psychiatry fit this profile of an ideal drug?

TABLE 1
PHARMACOKINETICS OF THE IDEAL AED

High oral bioavailability
No/low protein binding
Long half-life
Linear kinetics
No active metabolites
Renal elimination
No enzyme induction
No/few drug interactions

Adapted with permission from Gram.[4]

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TABLE 2
PHARMACOKINETIC CHARACTERISTICS OF THE NEWER AVAILABLE AEDs

Drug	Peak Absorption (h)	Bioavailability (%)	$T_{1/2}$(h)	Protein Binding (%)
Felbamate	2–6	> 90	15–23	25
Gabapentin	2–3	35–60	6–7	0
Lamotrigine	1–3	98	15–70	55
Topiramate	1–4	> 80	18–23	15
Tiagabine	1–2	100	5–8	96

Adapted from Gram.[4]

CURRENTLY MARKETED AEDS USED IN PSYCHIATRY

The pharmacokinetic characteristics and interactions of the newer AEDs are summarized in *Tables 2* and *3*. The benefit to be gained from these second-generation agents will be evaluated for their pharmacokinetic profiles, reduced incidence of adverse effects, and limited drug-drug interactions. Many of the newer agents do, indeed, have simpler pharmacokinetics and fewer drug interactions than the older AEDs. These parameters will be described in greater detail in the following sections.

Felbamate

Felbamate is a dicarbonate derivative that appears to potentiate the action of γ-aminobutyric acid (GABA) and to elicit postsynaptic blockade of the *N*-methyl-D-aspartate (NMDA) receptor.[5] It is the only one of the newer agents that is approved currently for use as monotherapy in the treatment of epilepsy.

Felbamate is rapidly and completely absorbed in a linear fashion after oral administration, reaching maximum concentrations in 2 to 5 hours; it exhibits a high bioavailability (> 90%).[6–8] The half-life has been estimated at approximately 20 hours,[6,7] which, theoretically, should allow for qd or bid administration. High doses frequently result in gastrointestinal complaints, so patients may tolerate it only when divided into three daily doses. Felbamate is metabolized in the liver. There is no evidence that felbamate induces liver enzymes, but it does inhibit the clearance of some other drugs.

Although protein binding is low (approximately 25%), felbamate is nonetheless associated with substantial drug interactions, particularly when combined with other AEDs. Polytherapy including felbamate has been shown to increase plasma concentrations of phenytoin,[9,10] valproate,[11] and carbamazepine epoxide and to decrease carbamazepine plasma levels.[9,10,12–14] In addition, comedication with phenytoin and carbamazepine reduces the felbamate concentration[15]; valproate may increase it.[11]

Felbamate is nonsedating, but complaints of insomnia, nausea, anorexia, and weight loss are common, and there have been reports of anxiety and psychosis.[16,17] Use of felbamate in the treatment of epilepsy significantly declined when it was reported to cause aplastic anemia and hepatic necrosis.[18,19] Its use will be limited in psychiatry as well because of these same complications.

Gabapentin

Gabapentin was developed by integrating GABA into a lipophilic cyclohexane moiety, in order to transport GABA across the blood-brain barrier. The goal was for this analogue molecule to inhibit seizures by binding to the GABA receptor. Gabapentin does have anticonvulsant activity but, in fact, does not adhere to the GABA receptor; instead, it is believed to bind to a novel site that has not been well characterized.[20]

The starting dose of gabapentin is 300 mg qd, increasing to 300 mg bid on day 2 and to 300 mg tid on day 3, with subsequent increases as needed. Gabapentin is rapidly absorbed (2 to 3 hours) following oral single-dose administration. Food has no effect on absorption. The bioavailability, estimated at 60%, can be variable due to the drug's dose-dependent absorption kinetics over the dose range 100 to 900 mg.[21] This dose dependence is probably related to the mechanism of absorption from the gut, which functions via a saturable L-system transporter for neutral amino acids.[22] The

TABLE 3
INTERACTIONS OF THE NEWER AEDS

Parent	Induces Metabolism of These Drugs	Inhibits Metabolism of These Drugs	Induces Parent Drug Metabolism	Inhibits Parent Drug Metabolism
Felbamate	CBZ	CBZ-E, PHT, PB, VPA	PHT, PB, CBZ	None
Gabapentin	None	None	None	None
Lamotrigine	None	None	PHT, PB, CBZ	VPA
Topiramate	Oral contraceptives	None	PHT, PB, CBZ	None
Tiagabine	None	None	PHT, PB, CBZ	None

CBZ=carbamazepine, CBZ-E=carbamazepine epoxide, PB=phenobarbital, PHT=phenytoin, VPA=valproic acid.
Adapted from Gram.[4]

nonlinear absorption profile is unique among the AEDs. This saturable transport mechanism may reduce the symptoms from overdose because the maximum drug absorption results in a lower plasma level.

The serum half-life of gabapentin is relatively short, at 6 to 7 hours. In the central nervous system (CNS), however, the effect of the drug appears to be longer than the serum half-life would suggest. Thus, the CNS efficacy is sustained beyond the duration of peak serum levels,[23] probably because of accumulation of gabapentin in the neurons. Gabapentin does not undergo hepatic metabolism in man and is excreted unchanged in the urine. Dose adjustments may be necessary in renally impaired patients.[24] Hemodialysis does increase clearance in anuric patients.[25] The absence of hepatic metabolism and zero protein binding prevents significant drug interactions, although alterations in gabapentin renal clearance have been observed with cimetidine,[21] and reduced absorption has been related to use of aluminum/magnesium hydroxide antacids.[26] There are no interactions with oral contraceptives.[21]

The most common adverse effects of gabapentin are somnolence, ataxia, dizziness, and fatigue. Significant side effects, however, are uncommon and rarely necessitate withdrawal of the drug.

Pregabalin, which is currently in clinical trials, is structurally similar to gabapentin, binds to the gabapentin-specific receptor, and may prove to be a more potent and longer-lasting analogue of gabapentin.[27] This compound will likely prove to have a role in neurology, psychiatry, and pain management as future research unfolds.[28]

Lamotrigine

Lamotrigine is a phenyltriazine derivative that inhibits voltage-gated sodium channels and reduces the release of glutamate. The anticonvulsant spectrum of this drug, however, is far broader than that of phenytoin and carbamazepine, which also work at the sodium channels. In addition, its psychiatric activity suggests additional mechanisms play a role in its clinical activity.

Lamotrigine is rapidly (1 to 3 hours) and completely absorbed, with almost 100% bioavailability.[29–31] It has moderate protein binding (56%) that is unaffected by other AEDs.[32] In monotherapy it has a half-life of 25 hours, but when administered with metabolism-inducing agents such as phenytoin or carbamazepine, the half-life drops to ≤ 15 hours.[30,33] When combined with a drug that inhibits its metabolism, such as valproic acid, the half-life can reach 60 hours.[33] This potential for drug interaction complicates its titration schedule (*Table 4*). Lamotrigine has no significant effect on plasma concentrations of other AEDs or on oral contraceptive efficacy.

Lamotrigine is conjugated in the liver. It follows linear kinetics, but to some extent has been shown to induce its own metabolism[34]; thus, with higher doses, where autoinduction is greater, the plasma concentration would appear to fall off somewhat on a kinetic curve.

Rash, similar to that observed with phenytoin and carbamazepine, can be a significant problem during lamotrigine therapy. In early clinical trials, roughly 8% of adults and 16% of children experienced a rash.[35] Serious rashes requiring hospitalization occur in < 0.5% of patients, but because they may lead to

TABLE 4
LAMOTRIGINE TITRATION SCHEDULE FOR ADULTS*

Without VPA but with enzyme-inducing AEDs
Add-on:
Begin 50 mg/d
Increase to 50 mg bid after 2 weeks
Increase by 100 mg every 1 to 2 weeks to maximum of 500 mg

With VPA and enzyme-inducing AEDs
Add-on:
Begin 25 mg every other day
Increase to 25 mg/d after 2 weeks
Increase by 25 to 50 mg/d every 1–2 weeks to 100 to 150 mg/d

*Note: New titration schedules for adults and children are under consideration by the manufacturer and the FDA. VPA = valproate.

Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema, all rashes should be regarded as serious. Early studies of lamotrigine were performed prior to the clarification of its interaction with valproate, and before slow titration was known to be a necessity.[35] Low starting doses and slow dose titration are important and markedly reduce the occurrence of rash in adults and children.

Topiramate

Topiramate is a sulfamate-substituted monosaccharide with influence at several neurologic sites. It inhibits rapid firing at voltage-dependent sodium channels, increases the effect of GABA at the $GABA_A$ receptor, and antagonizes kainate at the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor.[36]

Topiramate therapy is initiated at a dose of 25–50 mg/day and titrated with weekly 25-to 50-mg increases to an effective dose (usually 200–400 mg). It is well absorbed following oral administration,[36] although absorption may be slowed by food.[37] It has a half-life of approximately 20 hours, allowing bid dosing. The bioavailability exceeds 80%. It is largely unbound to plasma proteins and predominantly (80%) excreted unchanged in the urine in a linear manner, undergoing 20% hepatic oxidation (when given as monotherapy).[37]

Topiramate does not affect liver enzymes and has no effect on plasma levels of carbamazepine or valproate[38]; it can reduce clearance of phenytoin, however, by as much as 20% in some patients.[38–41] In the presence of metabolism-inducing drugs, topiramate becomes more extensively metabolized in the liver, and its plasma concentration and half-life fall by as much as 50%.[38–41] In addition, topiramate can interfere with the efficacy of oral contraceptive agents; women taking these drugs should be advised of this interaction and should consult with their gynecologist.

The main adverse effects of topiramate therapy[42] include somnolence, dizziness, ataxia, speech and cognitive disorders, and fatigue. Weight loss occurs in about 20% of patients. Cognitive symptoms—including difficulty with speech, memory, and language processing—are insidious and affect roughly 25% of patients. The cognitive side effects are the principal reasons why patients discontinue therapy with this drug.

Tiagabine

Tiagabine is a nipecotic acid derivative that blocks glial and neuronal reuptake of GABA, resulting in elevated extracellular GABA concentrations. Its mechanism is thought to be via intensification of inhibitory GABA-ergic transmission.[43]

Tiagabine is rapidly and well absorbed after oral administration,[44] reaching peak concentrations within 1 hour (food intake may slow absorption).[45,46] It is approximately 95% protein bound and extensively metabolized, probably in the liver by the P450 enzyme system.[47–49] The half-life during monotherapy is 8 hours.[48] Tiagabine is not itself an enzyme-inducing agent, but when added to enzyme-inducing medications, its clearance is increased and half-life reduced to 4 to 6 hours. It exhibits a linear excretion profile.[50]

Tiagabine does not appear to interfere with the metabolism of other AEDs,[51] but there is theoretic potential for pharmacodynamic interaction with other GABA-enhancing compounds. Tiagabine does not interfere with the efficacy of oral contraceptives,[52] but little is known about other drug-drug interactions. It is often prescribed with food to delay the extremely rapid absorption and thereby minimize side effects. The most common side effects of tiagabine are dizziness, somnolence, and tremor. It

may also cause confusion, as well as speech and language problems.

SUMMARY

The newer AEDs have potential in the treatment of psychiatric disorders. In light of this expanding spectrum of activity, it is necessary to refine and focus the safety and efficacy of the use of these agents among a wider population. The classic AEDs had numerous problems, ranging from inconvenient dosing schedules to frequent side effects due to active metabolites and common drug interactions; newer agents have been developed to avoid some of these pitfalls. Indeed, a generation of drugs that appears to have relatively simple pharmacokinetics and limited drug interactions—making them safer and easier to administer—is now available.

The use of these agents in psychiatry will necessitate additional investigation into their dosing and administration guidelines, as well as their interactions with other common psychiatric or concomitant drugs. Certainly, over time, they will be evaluated for these parameters in the newer indications. In the meantime, a review of the established pharmacokinetic and pharmacodynamic activities of these agents is the first step in defining their optimal uses and limitations in the psychiatric setting.

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Anticonvulsants for neuropathic pain and detoxification

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Anticonvulsants have been used for treatment of neuropathic pain almost as long as they have been used for seizures. Bergouignan successfully treated trigeminal neuralgia with phenytoin in 1942.[1] Though it subsequently became a standard agent for this pain disorder, phenytoin use was limited by the fact that it often loses efficacy over time, and the high doses required for therapeutic activity often cause unacceptable side effects. Nonetheless, this was the beginning of the current, widely accepted use of anticonvulsant drugs to treat neuropathic pain. Since the 1960s, anticonvulsant agents have been used extensively for pain management, particularly for lancinating or burning pain of neuropathic origin. Carbamazepine is one of the most effective drugs and often the first-line agent in the treatment of trigeminal neuralgia. But today, two drugs are expanding the utility of anticonvulsant drugs: valproate, which is better tolerated, and the newer agent gabapentin, which has a unique and safer pharmacokinetic profile. Although not officially approved for use in pain therapy, there is substantial documentation for the clinical efficacy of these drugs in the treatment of neuropathic pain syndromes.

Phenytoin also has a long history of use in the treatment of alcohol withdrawal seizures. Although the efficacy of phenytoin in easing alcohol withdrawal is now in doubt, some of the newer anticonvulsants have been shown to essentially reverse signs and symptoms of alcohol and sedative withdrawal. In this summary, the older drugs phenytoin, carbamazepine, clonazepam, and valproic acid, and two newer agents gabapentin and lamotrigine are discussed and their roles in neuropathic pain management and detoxification are reviewed.

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MECHANISMS OF THE AVAILABLE ANTICONVULSANT DRUGS

The use of anticonvulsant drugs to reduce neuropathic pain and to manage sedative withdrawal is based on their ability to decrease membrane excitability (either by interacting with neurotransmitter receptors or ion channels)[2] and to suppress discharges in pathologically altered neurons. The exact mechanisms by which they alleviate the sensation of pain are not fully understood. *Table 1* summarizes some of the sites of action that have been identified for the anticonvulsants used to treat pain and withdrawal.[2]

The known mechanisms of anticonvulsant agents[2] may provide some insight into their function in neuropathic pain and detoxification (the pharmacokinetics of the newer agents are reviewed by Morris elsewhere in this supplement). It is clear, however, that the mechanisms responsible for the anticonvulsant activity of these drugs are not the same as those that alleviate pain. This is evident in the fact that drugs such as barbiturates have no analgesic effect, despite being good anticonvulsants; similarly, phenytoin provides inferior pain control compared with other agents of equivalent or lesser anticonvulsant activity.[3,4]

TABLE 1
ANTICONVULSANT AGENTS: SITES OF ACTION

	Na Channel	$GABA_A$ Channel	T-Ca Channel	NMDA Channel
Older agents				
Carbamazepine	++	—	—	
Phenytoin	++			
Valproic acid	++	?/+	?/+	
Barbiturates	+	+	—	
Benzodiazepines	+	++	—	
New agents				
Felbamate	+	—	?	+
Gabapentin	+	—		?
Lamotrigine	++	—	?	?

From MacDonald and Kelly,[2] with permission

NEUROPATHIC PAIN: CHARACTERISTICS AND DIAGNOSIS

What is neuropathic pain?

It is useful to distinguish "normal" from pathologic pain. The neurologic systems that signal pain function appropriately when there is a close correspondence between the intensity of a mechanical, thermal, or chemical stimulus and the degree of pain as perceived by the individual. Such "normal" pains signal real or potential damage to bodily integrity, and they respond to treatment with the classic analgesic agents, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

When there is damage to this signaling system, signals disproportionate to the provoking stimulus, or absent of any peripheral stimulus, arrive at the central nervous system (CNS). These pathologic pains are often poorly responsive to typical analgesics; instead, they may respond to treatment with antidepressant, anticonvulsant, or antiarrhythmic medications. Significantly, the response of these pains to pharmacotherapy seems less dependent on the etiology of the neuropathology than on underlying pathophysiology of the pain state. For this reason, a clinician seeking guidance in treating a traumatic nerve lesion with allodynia should rely more on drug trials in allodynia than on studies of nerve trauma.

Pathophysiology of neuropathic pain

Virtually any condition that damages neural tissue or impairs its function can be a source of neuropathic pain. Thus, injury, inflammation, ischemia, metabolic derangements, toxins, tumor, and primary neurologic diseases may lead to mononeuropathy, polyneuropathy, or CNS sources of neuropathic pain. In fact, a combination of processes frequently contributes to the symptom of pain following nerve injury. For a thorough review of the pathophysiology of neuropathic pain, refer to Bennett[5] or Devor.[6]

Identification of neuropathic pain

Neuropathic pain may be suggested first by pain in an apparently healthy body part, such as the electrical pain that shoots down the leg in sciatica. In addition, certain sensations (eg, burning, electrical, paroxysmal, jabbing, squeezing, deep aching, spasmodic, or cold) or sensory perversions (eg, paresthesias, formication, broken glass sensation, or allodynia) are indicative of neuropathic origin. Sensory loss is often present. The pain may be unresponsive to maneuvering, repositioning, etc.

The distribution of pain often is diagnostic. Thus, hemibody pain may result from cortical, internal capsule, or thalamic lesions, while pains that follow the distribution of cranial or somatic nerves suggest damage to these structures. Frequently, a pain drawing created by the patient is nearly diagnostic. Complex regional pain syndrome (reflex sympathetic dystrophy) is marked by allodynia, autonomic changes (temperature, color, sweating), and trophic changes (skin, hair, nails). Furthermore, neuropathic pain is often resistant to treatment with NSAIDs and opioids.[7–9]

More difficult cases to identify are those in which frequent, intense prior nociception has led to central sensitization causing specific structures to become painful. For example, intraspinal ligament injection with saline may cause chest wall hyperalgesia in humans, and in animal studies, rectal or vaginal inflammation leads to prolonged hyperalgesia in these areas, as well as in their associated somatic referral areas. Visceral hyperalgesia is thought to explain some obscure chronic abdominal pains that follow illnesses or surgeries.[10–12]

ANTICONVULSANT AGENTS: USE IN PAIN MANAGEMENT

It is somewhat remarkable, given the long history of anticonvulsant use in chronic pain, that most of the applications of these agents are based on anecdotal reports in humans, at times bolstered by experience in animal models. Almost every source of neuropathic pain has been treated with anticonvulsants in at least a few patients, but there have been few controlled, blinded, randomized trials.

The best-studied neuropathic pain, and the only one for which anticonvulsants have an approved indication, is trigeminal neuralgia. By extension, however, this use led to testing of anticonvulsants for most neuropathic pains characterized by paroxysms. If the pain description suggested a ganglion or nerve "seizure," anticonvulsants were administered, generally with excellent (anecdotal) results. Glossopharyngeal and other cranial neuralgias were convincingly shown to respond to anticonvulsants, as were lightning pains of tabes dorsalis and similar pain in multiple sclerosis.[3] In a review of controlled trials of anticonvulsants for neuropathic pain, McQuay and coworkers[13] found good evidence that anticonvulsants provided effective treatment for trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis; other uses have been reported as well (*Table 2*).

Clinical applications for the various anticonvulsants are reviewed below.

Phenytoin

An animal model for use of phenytoin in neuropathic pain has been described.[14] In rats with sciatic nerve neuromas, systemic administration of phenytoin suppressed spontaneous impulse discharge, which is thought to be a cause of paresthesias and pain following nerve injury. Although phenytoin was the first anticonvulsant used for the treatment of human neuropathic pain, it is often not the best. For example, Swerdlow[3] reported that 70% of patients with trigeminal neuralgia responded to carbamazepine, whereas only 20% improved with phenytoin. Kingery[4] extensively reviewed the literature on drug treatment of neuropathic pain, concluding that carbamazepine was efficacious but the data for phenytoin were contradictory. Phenytoin has been used for many other conditions, including diabetic neuropathy,[15] Fabry's disease, tabetic lightning pain, and thalamic pain; however, newer anticonvulsants are probably better first-line agents.

TABLE 2
SETTINGS IN WHICH ANTICONVULSANTS HAVE BEEN USED FOR PAIN RELIEF

Trigeminal, cranial neuralgia[3]
Postherpetic neuralgia[3]
Tabes dorsalis (lightning pain)[3]
Myelopathy*
Phantom limb pain[3]
Thalamic pain[3]
Plexus avulsion[3]
Diabetic neuropathy[3,44]
Migraine prophylaxis[3]
Multiple sclerosis[3]
Poststroke pain[3]
Traumatic neuropathy[3]
Tumor invasion, compression[3]

From Swerdlow[3] and Backonja[44]
*From Wetzel CH, Connelly JF. Use of gabapentin in pain management. Ann Pharmacother 1997; 31:1082–1083.

Carbamazepine

Carbamazepine is perhaps the most studied anticonvulsant for pain management. It is approved for use in trigeminal neuralgia and is promoted as therapy for glossopharyngeal neuralgia. Although carbamazepine was originally primarily used for paroxysmal pains, such as tabetic lightning pains, its use subsequently extended to include such pains as diabetic neuropathy,[16] postherpetic neuralgia,[17] phantom limb pain,[18] and multiple sclerosis.[19]

In one study, a minority of patients with brachial plexus avulsion responded to treatment with carbamazepine, suggesting that other agents might be used first for this condition.[20] Blom[21] found carbamazepine to provide superior pain relief in trigeminal neuralgia compared with phenytoin. In a double-blind, controlled crossover trial involving 15 patients with central poststroke pain, Leijon and Boivie[22] reported that 10 patients responded to amitriptyline 75 mg/day compared with five who responded to carbamazepine 800 mg/day. The benefit of carbamazepine was not statistically significant when compared with placebo. In addition, carbamazepine caused more side effects than amitriptyline.[22] Based on a review of anticonvulsant agents used in the treatment of postherpetic neuralgia, Watson concluded that the activities of carbamazepine, phenytoin, and valproic acid were either unimpressive or difficult to interpret due

to antidepressant coadministration.[23] Carbamazepine was not effective in rat allodynia after cord ischemia, whereas tocainide was efficacious.[24] Thus, the human and animal literature confirms that carbamazepine is efficacious for some, but not all, neuropathic pains, and in many clinical situations its use is based more on suggestions of efficacy than on conclusive studies.

The clinical application of carbamazepine may be limited in the long term by some serious, albeit uncommon, adverse effects. Aplastic anemia, agranulocytosis, thrombocytopenia, hepatic abnormalities, and dermatitis may develop during carbamazepine use.[25] Furthermore, carbamazepine is a potent enzyme inducer, capable of inducing its own metabolism. It is associated with frequent drug-drug interactions, necessitating cautious administration, especially among patients receiving several concomitant medications.[26]

Valproic acid

Although used to treat trigeminal neuralgia and postherpetic neuralgia, the best studies of valproic acid use involved patients with headache.[27] Rothrock et al[28] treated 75 patients with intractable headache with valproic acid and reported response rates of 61%, 51%, and 21% in the treatment of frequent migraine, transformed migraine, and tension-type headache, respectively. In a triple-blind, placebo-controlled, crossover trial, Jensen et al[29] found that 65% of 43 migraine patients responded to prophylactic treatment with valproic acid by week 4. The number of days with migraine decreased 43% with active treatment compared with placebo. The severity and duration of those headaches that did occur, however, were unaffected.[29]

Cutrer and colleagues[30] found that valproic acid reduced c-fos expression in guinea pigs given intracisternal capsaicin, an irritant. This effect was blocked by $GABA_A$ antagonists but not by $GABA_B$ antagonists, suggesting that valproic acid blocks neurogenic inflammation within the meninges via a $GABA_A$ receptor-mediated mechanism.

Valproic acid is generally well tolerated, although a number of adverse effects, some serious, complicate its use. The most common side effects involve gastrointestinal disturbances, which are often effectively treated with histamine antagonists. The most serious adverse effects are potentially fatal hepatotoxicity which occurs most often in children and individuals with prior liver disease and, rarely, pancreatitis. Of more concern are frequent endocrinological effects including polycystic ovaries.[31]

Clonazepam

Clonazepam is used to alleviate pain due to cranial neuralgias, postlaminectomy, phantom limb, amputation stump, postherpetic neuralgia, multiple sclerosis, and peripheral neuropathy.[32,33] Caccia found it to be effective in five of seven patients with trigeminal neuralgia,[34] and Smirne and Scarlato reported benefit in 64% of patients with sphenopalatine neuralgia.[35] In an open study of deafferentiation pain, Bouckoms and Litman[36] found that patients with allodynia responded better to clonazepam than those without allodynia.

The use of benzodiazepines in pain management is complicated by adverse effects on mood and cognition, and risk of addiction among individuals with a history of chemical dependency. There has been concern as well that benzodiazepines may increase pain during chronic use; in the acute situation, postoperative pain was reduced by administration of flumazenil, a benzodiazepine antagonist, among individuals who had been given preoperative diazepam.[37] For these reasons, benzodiazepines are rarely drugs of first choice for the treatment of pain.

Gabapentin

Despite few controlled studies on the efficacy of gabapentin in human pain management, this new drug has become the anticonvulsant of choice among many pain specialists. This popularity probably reflects promising studies in animals showing efficacy in disparate pain states, a low side effect profile, and lack of drug interactions in patients with pain, who often are subject to extensive polypharmacy.

Animal models provide strong support for the analgesic efficacy of gabapentin in several types of pain. Mechanical allodynia in rat models of causalgia was relieved by gabapentin administration.[38] Gabapentin's efficacy was reported as well by Hunter et al,[39] who compared lamotrigine, felbamate, and gabapentin in rat models of acute and neuropathic pain (chronic constriction injury and spinal nerve ligation). Lamotrigine, felbamate, and gabapentin reversed cold allodynia; however, only gabapentin ameliorated tactile allodynia. Interestingly, carbamazepine and phenytoin were ineffective in both models. The gabapentin doses required for antiallodynic activity had virtually no

effect on acute nociception and did not affect locomotion. Shimoyama et al[40] found that gabapentin administered intrathecally prevented hyperalgesia from occurring after intraplantar formalin administration. Thus, in animal models gabapentin is analgesic in various types of neuropathic pain, suggesting wide clinical applicability.

There are several reports of gabapentin's efficacy in mixed neuropathic pain.[41,42] In addition, Mellick and Mellick[43] reported six cases of intractable complex regional pain syndrome that responded well to gabapentin therapy. In a double-blind study, gabapentin effectively alleviated pain from diabetic neuropathy.[44] It has been tried with some success, as well, in postherpetic neuralgia, thalamic pain, and erythromelalgia.[45]

Gabapentin is notable for its lack of drug interactions, simple elimination pathway, and lack of adverse reactions. It does not require monitoring via hematologic or liver studies. Although it produces ataxia, sedation, and cognitive slowing, these effects generally do not occur at clinically appropriate doses. Weight gain and constipation may be problematic.[46]

Lamotrigine

Lamotrigine, like gabapentin, effectively relieves pain of varying neurophysiologic causes. Nakamura-Craig and Follenfant[47] found that in rats, lamotrigine blocked the hyperalgesia induced by plantar injections of prostaglandin E_2 as well as by diabetes. This contrasts with the results of Chapman et al,[48] who compared the effects of lamotrigine and bupivacaine on central sensitization produced by electrical stimulation of C fibers. Lamotrigine was found to enhance windup and postdischarge, which occur in dorsal horn neurons in this model; bupivacaine reduced both. As a result, lamotrigine facilitated C fiber-evoked responses, raising questions about the potential of lamotrigine as an analgesic. This remains to be clarified by future research or clinical reports.

The clinical applications of lamotrigine have included trigeminal neuralgia, postherpetic neuralgia, and central pain. In a double-blind, crossover trial, Zakrzewska et al[49] continued carbamazepine or phenytoin therapy among patients with refractory trigeminal neuralgia and added lamotrigine 400 mg/day or placebo. Eleven of fourteen patients achieved significant benefit from the addition of lamotrigine, as assessed by pain scores and use of escape medications.[49] In another trial, Canavero and Bonicalzi[50] successfully treated four patients with central pain (two from cerebrovascular accident, one due to brain tumor, and one from cervical syrinx) with lamotrigine up to 600 mg/day. Lamotrigine provided relief of burning, lancinating, electrical, and allodynia pain among these patients who had been refractory to treatment with carbamazepine and valproic acid. In addition, Canavero and colleagues[51] reported 90% relief of trigeminal neuralgia among four patients treated with lamotrigine in an open-label design.

SPECIAL CONSIDERATIONS

Due to the novel use of drugs normally indicated for seizure disorders in the treatment of neuropathic pain, several adaptations from standard practice must be observed. Patients should be advised of the fact that this is an off-label use of these medications in order to avoid confusion with the pharmacist, who might assume a seizure disorder. It is also necessary to explain that, since response to these agents is not predictable, serial trials may be required to ensure optimal relief. Furthermore, dose requirements for pain treatment are not established, making it necessary to start at a minimum dose and titrate to optimal response or toxicity. In cases for which combination therapy is necessary involving antidepressant, anticonvulsant, and/or antiarrhythmic medications, it is important to titrate one drug at a time.

ANTICONVULSANT AGENTS: USE IN SEDATIVE DETOXIFICATION

Anticonvulsant agents have been investigated as treatment for sedative withdrawal since 1976.[52] Results from early studies suggested a trend toward efficacy in managing withdrawal symptoms (*Table 3*),[53–59] and subsequent studies established the value of valproic acid, carbamazepine, gabapentin, and clonazepam in specific withdrawal settings. The accumulated literature on anticonvulsant use during detoxification is reviewed below.

Carbamazepine

In 1986, Klein and coworkers[60] reported three cases in which carbamazepine attenuated alprazolam withdrawal symptoms. In a case review series, Ries and colleagues[61] reported that carbamazepine permitted rapid detoxification among patients tak-

TABLE 3
EARLY EXPERIENCE WITH USE OF ANTICONVULSANT AGENTS DURING SEDATIVE WITHDRAWAL

Drug	No. Pts.	Control	Results	Comments
Carbamazepine				
Bjorkqvist et al[53]	105	Placebo	CBZ > P	More returned to work with CBZ
Riitola, Malinen[54]	68	CMT	Equivalent	70% response
Agricola et al[55]	60	Tiapride	Equivalent	CBZ faster acting
Flygenring et al[56]	60	Barbital	Equivalent	Both well tolerated
Malcolm et al[57]	86	Oxazepam	Equivalent	Psych symptoms improved more rapidly with CBZ
VPA				
Lambie et al[58]	48	CMT±VPA	VPA group needed	No statistical analysis
Carbamazepine + VPA				
Hillbom et al[59]	138	VPA vs CBZ	Side effects frequent	High incidence of side effects with both due to rapid dose

CBZ=carbamazepine; P=placebo; CMT=clomethiazole; VPA=valproic acid
From Keck et al,[52] with permission

ing high doses of those benzodiazepines that cause severe abstinence syndromes (eg, alprazolam 10 mg/day). Although supplemental benzodiazepines were available as needed for withdrawal symptoms, none was required.

In a double-blind study involving 40 patients with difficulty discontinuing daily benzodiazepine use, Schweizer et al[62] found that the addition of carbamazepine 200 to 800 mg/day permitted comfortable detoxification over 5 weeks. In addition, more carbamazepine-treated patients remained free of benzodiazepines at 5 weeks, suggesting that subtle symptoms of protracted withdrawal also may be reduced. Carbamazepine treatment appeared most beneficial for patients receiving dosages equivalent to > 20 mg diazepam.

Malcolm and colleagues[57] compared the efficacy of carbamazepine 800 mg/day with oxazepam 120 mg/day in detoxifying 86 men with severe alcohol withdrawal. The drugs were equally effective, but global psychologic distress increased among those taking oxazepam, whereas it declined in those taking carbamazepine. These findings suggest that carbamazepine is as effective and safe as benzodiazepine treatment for alcohol withdrawal syndrome. It, of course, offers a significant advantage if symptoms of protracted withdrawal require treatment, as patients can be maintained on nonaddicting medication.

Valproic acid

Valproic acid has been successfully used in the treatment of benzodiazepine withdrawal, as described in case reports and one small series.[63,64] Roy-Byrne et al[65] described a patient who had been unable to discontinue alprazolam intake, even at extremely slow rates, but who was comfortably withdrawn with the addition of valproic acid. In 1980, Lambie et al[58] randomly assigned alcohol-dependent individuals to treatment with valproic acid 400 mg vs no treatment as add-on to conventional medications for detoxification. Withdrawal symptoms decreased more rapidly and less conventional medication for withdrawal was required by those patients receiving valproic acid.

Hillbom and colleagues[59] found that treatment with carbamazepine and valproic acid produced a high incidence of side effects, perhaps hampering their utility as treatment for alcohol withdrawal symptoms; however, this may have resulted from aggressive dose titration.

Gabapentin

Animal models. Watson and associates[66] found that gabapentin, in doses that did not impair locomotion or coordination, reduced anxiety and induced an anticonvulsant response in alcohol-dependent mice experiencing withdrawal. By contrast, phenytoin failed to provide benefit, carba-

TABLE 4
RESPONSE AMONG SEVEN PATIENTS TO GABAPENTIN THERAPY DURING SEDATIVE WITHDRAWAL

Age/sex	Diagnosis	Dependence	Baseline Diazepam Equivalents (mg/day)	Maximum Dose (mg/day)	Discontinuation Dose (mg/day)
66/F	Mixed headache	BZD	50	1200	400
34/M	Atypical face pain	BZD	40	2400	2400
32/F	Pelvic pain	BZD	80	1200	None
32/F	Mixed headache	PB	20	1200	600
38/M	Lumbar canal stenosis	BZD	40	1600	1200
76/F	Postherpetic neuralgia	BZD	25	2400	2400
51/F	Fibromyalgia, headache	BZD	80	3600	1000

BZD=benzodiazepine; PB=phenobarbital
From Covington et al[68]

mazepine reduced symptoms only at intoxicating doses, and valproic acid was effective only at sedating doses. Based on this finding, it was theorized that the gabapentin binding site may be selectively affected by alcohol withdrawal, because the dose required for withdrawal control is lower than that required to prevent seizures from other causes.

Bailey et al[67] studied alcohol withdrawal response in hippocampus slices from rats. As compared with controls, brain slices from animals undergoing alcohol withdrawal had reduced thresholds for production of single- and multiple-population spikes by electrical stimulation, as well as "reverberative firing patterns." These changes were prevented in large by gabapentin and isradipine (a calcium channel antagonist). Neither drug altered thresholds in normal (not undergoing alcohol withdrawal) brain slices.

Clinical use. We have found gabapentin to be effective in the treatment of benzodiazepine and sedative withdrawal in a group of patients with chronic pain.[68] This trial was prompted by the following anecdotal experience. A 66-year-old patient with intractable headache who was being withdrawn from butalbital and alprazolam was unsuccessfully treated with clonazepam. Switching to valproic acid was effective, but resulted in SIADH (sodium of 119 mmol/L). A subsequent trial of carbamazepine 800 mg/day caused severe pruritic rash requiring discontinuation. A test dose of 300 mg gabapentin relieved the withdrawal symptoms and the patient continued therapy at 300 mg qid with good control.

In six of seven subsequent patients it was found that gabapentin successfully controlled sedative withdrawal symptoms *(Table 4)*.[68] The single failure probably resulted from inadequate dosing of gabapentin, an inference drawn from our current practice, which is to abruptly stop all benzodiazepines and barbiturates on admission and replace with gabapentin administration. Typically, treatment is started with a 300–800-mg test dose, depending on the patient's estimated degree of physical dependence and severity of predicted withdrawal syndrome. An additional 300–400 mg is given in an hour if there are no adverse effects and signs of withdrawal persist. Typically, patients are comfortable and free of significant withdrawal on gabapentin doses of 1800–4800 mg/day.

Phenytoin

Most studies of phenytoin in alcohol withdrawal address only the issue of seizure treatment or prophylaxis and not other components of the withdrawal syndrome. One group found that in alcohol-dependent mice phenytoin increased body tremor and other withdrawal signs, although it slightly ameliorated withdrawal from barbital.[69] The American Society of Addiction Medicine Committee on Practice Guidelines has taken the stand that phenytoin is not effective for alcohol withdrawal, even in the presence of a seizure.[70] The use of phenytoin is

reserved for cases in which there is an independent seizure disorder for which phenytoin is indicated, or to abort status epilepticus. In alcohol-dependent individuals with a history of withdrawal seizures, the evidence is considered inconclusive.

SUMMARY

It is now well demonstrated that several anticonvulsants have a role in the treatment of neuropathic pain and also in withdrawal from benzodiazepines, sedatives, and perhaps alcohol. Valproic acid, carbamazepine, gabapentin, clonazepam, and lamotrigine are appropriate treatments for neuropathic pain, effective to a degree dependent on the underlying pathophysiology. While less effective than newer agents, there are situations in which phenytoin remains useful. Currently, a limited understanding of both the processes responsible for pain and the specific effects of each agent prevents prediction of individual response to these drugs, often necessitating trials of several drugs before the best one is found. It is interesting that the anticonvulsant drugs most useful for neuropathic pain are the same ones effective in sedative withdrawal, bipolar disorder, and several anxiety disorders. Issues of neural hypersensitivity and kindling, therefore, may prove to be unifying concepts for these conditions.

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Bipolar disorder: Current treatments and new strategies

GARY S. SACHS, MD, AND VICTORIA E. COSGROVE, BA

Bipolar disorder is a complex, potentially lethal, chronic disease. The diversity of its symptoms presents clinicians with an ongoing challenge to make the correct diagnosis, to successfully manage the acute episodes, and to decide on a course for prophylaxis. Lithium, the first effective drug for bipolar disorder, is still considered the drug of choice for treatment of the acute phase and for maintenance. Although lithium has been the mainstay of bipolar treatment for half a century, the problem of managing many bipolar patients is unresolved, and other therapeutic agents are being investigated.

This paper will review issues concerning the diagnosis and epidemiology of bipolar disorder, discuss the unique problems of treating bipolar patients, and address the question of why lithium has not been working for many of them. It will analyze recent studies on the efficacy of anticonvulsants in the treatment of bipolar disorder and evaluate their use in prophylaxis and as mood stabilizers.

BIPOLAR DISORDER

Clinical presentation

Bipolar disorder, also known as manic depression, is characterized by recurrent periods of abnormal mood elevation alternating with periods of depression. During manic periods of euphoria and agitation, patients may display impaired judgment and irresponsible and frenzied behavior that is possibly injurious to themselves and others.[1] Each phase lasts from days to weeks. Rapid cycling individuals have at least 4 episodes of mood disturbances in a 12-month period. Some patients may suffer from mixed episodes, presenting simultaneously with both depression and mania.[1] The Massachusetts General Hospital (MGH) Bipolar Clinic defines continually cycling patients as those who go from one phase to another three or more times in a month without intermittent periods of euthymia.

Individuals with bipolar disorder can be a risk to themselves and to society. They are prone to child abuse and spousal abuse, and 10% to 15% of patients commit suicide. Other associated problems include school failure, occupational failure, divorce, and substance abuse.[1] The multiplicity of symptoms presented by bipolar patients complicates the process of diagnosis and the charting of treatment.

Epidemiology

Many symptoms characteristic of bipolar illness, like grandiose and persecutory delusions, impulsivity, and irritability are common to those observed in other psychotic disorders.[1] Therefore, cases of bipolar disorder are underdetected, with reported prevalence rates varying: 0.46% in the Old Order Amish Study,[2] 0.7% to 1.6% in a study of five communities,[3] and 0.9% to 2.1% reported in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[1] In addition, Weissman et al[3] reported no significant gender differences in either the prevalence or the age of onset of bipolar disorder.

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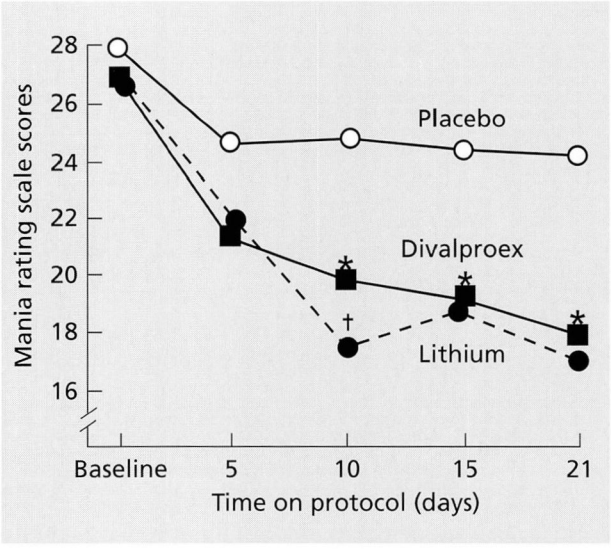

FIGURE 1. Changes from baseline to final evaluation in Mania Rating scale score, Schedule for Affective Disorders and Schizophrenia. Numbers on the vertical axis indicate the sum of all items on this subscale of the SADS-C. Asterisks and dagger indicate time points at which a significant difference ($P < .05$) was observed between divalproex and lithium, respectively, and placebo. Adapted from Bowden et al, 1994.[10]

Issues facing psychiatrists

Left untreated, bipolar disorder is dangerous for patients and for society. However, millions of bipolar patients receive no mental health care.[4] One approach for improving public health is to increase diagnosis and ensure that patients stay with treatment.

The major goal of treatment is to induce and sustain remission. Although the objective is the same as for any other mental disorder, treatment of bipolar disorder presents a unique set of problems. Effective treatment addresses both acute mania and acute depression and attempts to prevent both from recurring. A need for acute treatment may compete with a long-range goal of minimizing exposure to cycle-promoting agents. Treatment of a manic episode with antimanic agents may increase the risk of treatment-emergent depression. Treatment of a major depressive episode with antidepressants may induce mania.

LITHIUM TREATMENT

The use of lithium for the treatment of depression goes back to the 1880s. Lithium fell into disrepute because of toxicity associated with its misuse, but it was rediscovered by Cade in 1949 as an effective treatment for acute mania. Lithium was extensively used in Europe in the 1950s and 1960s.[5] In the United States, lithium was approved by the FDA as treatment for acute mania only in 1970, on the strength of placebo-controlled clinical studies demonstrating its efficacy.[6] In 1974 the FDA approved lithium as a maintenance drug for bipolar disorder.[7] In 1985 the NIH/NIMH Consensus Development Panel[8] recommended lithium as the drug of choice in the prevention of recurrent bipolar disorder, and the Expert Consensus Guidelines suggested lithium as the only first-line antidepressant to be used as a mood stabilizer in monotherapy.[9] Taking note of recent reports casting doubt on the efficacy of lithium as an antidepressant, the Expert Consensus Guidelines note that other mood stabilizers are even weaker.[9]

Efficacy for mania patients

More recent data suggest that the problem of treating bipolar patients has not been solved by the use of lithium. Bowden et al compared the efficacy of divalproex versus lithium and placebo in hospitalized, acutely manic patients in a randomized, double-blind, parallel-group study.[10] As shown in *Figure 1*, there was a significant improvement at 21 days for patients receiving either lithium or divalproex compared with patients receiving placebo. By the end of 21 days, patients' average score on the mania rating scale was 16. However, patients entering into the study were required to have a washout score of at least 14.[10] This indicates that after 21 days of treatment, they still were considered ill enough to enter the study.[10] Thus, although lithium and divalproex were efficacious, the benefit patients derived from them was not sufficient.

Prophylactic efficacy

A number of prospective studies suggest that the majority of bipolar patients do not benefit from the prophylactic agents in current use.

In a double-blind, multicenter, long-term follow-up study, the NIMH collaborative study group evaluated the prophylactic effects of lithium and imipramine in 117 bipolar patients.[11] Only 33% of patients receiving lithium monotherapy remained well for the 2-year duration of the study.[11] A 1-year follow-up study with patients receiving lithium

monotherapy in our MGH Bipolar Clinic showed that only 4% of patients remained well for the entire year. In addition, similar results were obtained in an evaluation of patients in private practice, ruling out the possibility that the poor outcome in the clinic was because the clinic patients were more seriously ill.[12]

Gitlin et al[13] noted that naturalistic studies of populations treated for bipolar disorder suggest greater morbidity and less evidence for successful prophylaxis with mood stabilizers than do earlier control studies. For a mean of 4.3 years, Gitlin et al prospectively followed 82 bipolar patients who were prescribed mood stabilizers in an uncontrolled manner in order to evaluate the efficacy of mood stabilizers in a clinic setting.[13] Analysis of the data showed 37% probability that a manic or depressive episode would occur within 1 year, 55% likelihood of a relapse within 2 years, and 73% chance of relapse within 5 years. Moreover, more than 70% of the patients who relapsed had multiple episodes.[13]

In a 5-year prospective study, Maj et al[14] interviewed 359 bipolar patients given lithium prophylaxis. Of the 247 patients still taking lithium at the 5-year follow-up, 15.4% showed no improvement, 46.6% had partial improvement, and 38.1% had no recurrence of a major depressive or manic episode. However, more than one third of this group had a subsyndromal affective morbidity during the treatment period. Only 14.2% of the patients evaluated had no affective morbidity.[14]

The contradictory results of early placebo-controlled studies of lithium and the more recent open studies, as well as evidence that divalproex alleviates acute mania, stimulated Bowden et al to design a 1-year outcome study comparing the effects of prophylactic treatment with lithium, divalproex, and placebo in bipolar patients.[15] Patients who had a manic episode within 3 months of randomization and had achieved remission within 3 months of enrollment, with or without any open treatment indicated by their physicians, were enrolled in this randomized, double-blind, parallel-group study.[15]

By the end of 1 year, 24% of patients on divalproex, 33% on lithium, and 39% on placebo suffered either mania or depression. These differences were not significant. Occurrence of mania alone was not significantly different among groups either; mania occurred in 18%, 22%, and 23% of the enrollees on divalproex, lithium, and placebo groups, respectively. Divalproex (6%) had a better prophylactic effect than lithium (10%) and placebo (17%) only in depression.[16] The high dose of lithium prescribed (1.0 ± 0.48 mmol/L) may account for the increased level of depression in the lithium group.

Taken together, the naturalistic and the controlled studies suggest that prophylactic medication is helpful for only 4% to 33% of bipolar patients.

Noncompliance

A major problem in lithium treatment is noncompliance, some of which is related to the perceived toxicity of lithium.[5] Although the prescribed doses are not toxic, the gap between the therapeutic and the toxic doses of lithium is the narrowest of any drug prescribed to psychiatric patients, and an overdose could cause severe damage.[10] The noncompliance rate in outpatients ranges from 12% to 60%.[17] Maj et al[14] found that 112 of 359 (31%) patients in longitudinal studies stopped taking lithium, and 85% of these did so on their own.

The most discouraging report on noncompliance in the use of lithium is the 6-year longitudinal cohort study by Johnson and McFarland of 1,594 patients enrolled for 6 months in a health maintenance organization (HMO).[18] Seventy-four patients in a random sample of the large group took lithium for an average of 34% of the days they were enrolled in the HMO, and only 8% of the patients were using it for 90% of their days of eligibility.[18] Reasons for noncompliance include uncomfortable side effects, stigma, patients' beliefs that they are well, and beliefs that treatment is unhelpful.[14,17]

Nonresponding patients

Patients who discontinue treatment with lithium because they feel well often relapse. Their sense of well-being may, in fact, be the prodrome: hypomania before mania. Rather than increase the lithium dose, which may exacerbate deterioration and drive compliance further down, clinicians should consider the possibility that these patients do not respond to lithium. The use of lithium adjuncts or substitutes should be considered.

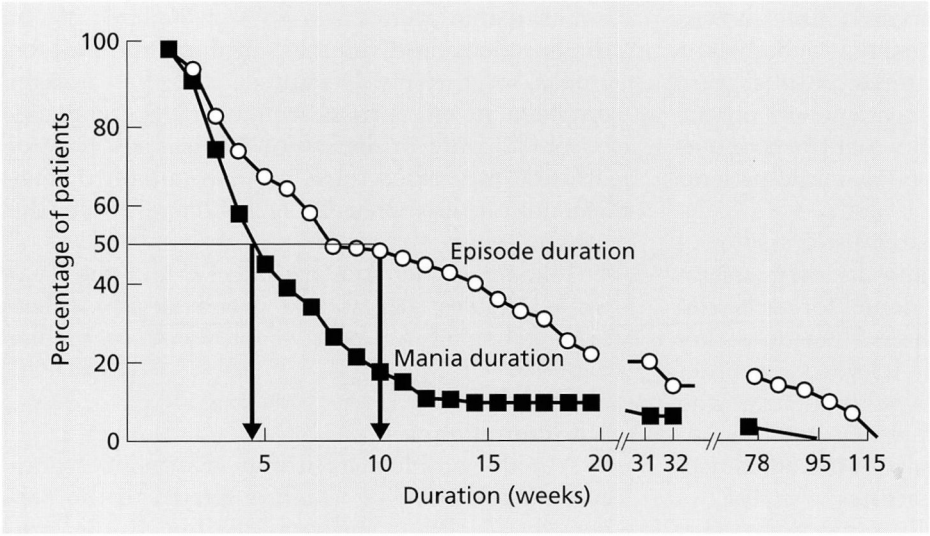

FIGURE 2. Duration of manic phases and episodes in bipolar patients at Massachusetts General Hospital Bipolar Clinic.

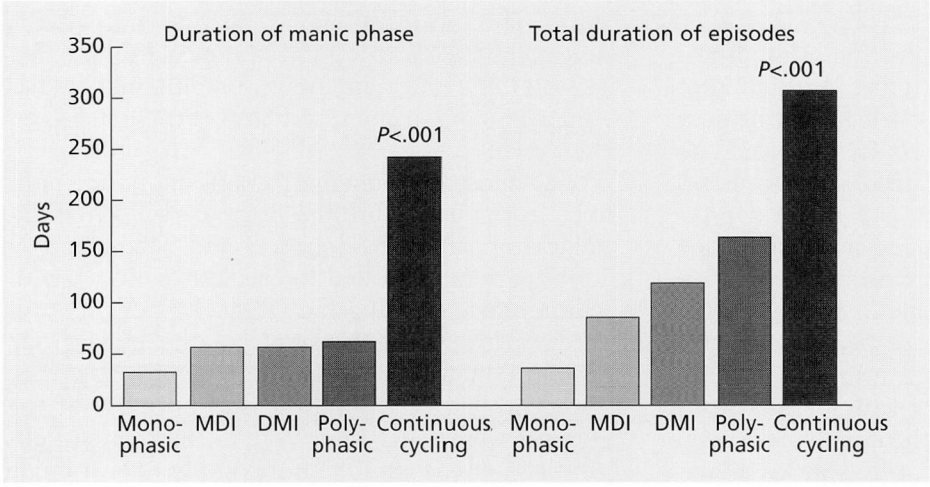

FIGURE 3. Episode pattern influence on episode duration. MDI = mania phase followed by depression, and interval of well-being; DMI = depression phase followed by mania, and interval of well-being. *P* values indicate difference between continuous cycling and any of the other four patterns.

The data from our MGH Bipolar Clinic (*Figure 2*) clearly illustrate the problems clinicians face. The manic phase in 50% of our patients persists for fewer than 5 weeks. Here, good outcome reflects good treatment. However, many of these patients suffer a relapse within a year. On the other hand, 15% to 20% of the episodes persist for 1 to 2 years. What can we do for these individuals?

Pattern of episodes as an indicator of treatment outcome

Dunner and Fieve[19] observed that bipolar patients on lithium prophylaxis with at least four affective episodes in a year (rapid cyclers) had a disproportionately high rate of relapse. Although the rate of treatment failure was 41% in nonrapid cyclers (18/44), the rate of relapse in the rapid cyclers was 82% (9/11).[19]

In our bipolar clinic at MGH we found correlations between the pattern of episodes, the duration of episodes (*Figure 3*), and the prognosis. Some groups of patients tend to have good prognoses—people who have monophasic episodes of mania, people with biphasic episodes that start high and go to depression (MDI) or begin with depression and go to mania (DMI), and people who have a chain of phases lasting at least 2 weeks each. The episodes of individuals who are continuously cycling last significantly longer ($P < .001$) than the episodes in patients presenting with any of the other four patterns. The prognosis for continuously cycling patients is not good. As soon as we identify such a pattern, we immediately follow our treatment algorithm and add other medications.[20]

As psychiatrists, we are faced with a great challenge: How can we help our bipolar patients who do not respond to lithium or divalproex? Antidepressants are often a poor option. Ideally, we would like to use mood stabilizers.

MOOD STABILIZERS

I would like to present a definition for what a mood stabilizer should be. A mood stabilizer should be efficacious for one or more of the primary therapeutic objectives in treating bipolar patients:

- Treating acute mania
- Treating acute depression
- Prophylaxis.

When administered during any phase of the illness, a mood stabilizer:

- Should not make the patient acutely worse
- Should not increase the switch rate between phases.

Agreeing on a definition for a mood stabilizer still does not help us in our quest for the ideal treatment. As much as we like to practice polypharmacy, not much data are present to tell us which drugs are mood stabilizers. The published guidelines in the *Journal of Clinical Psychiatry*[9] and our own guideline[20] show an approximate 93% agreement about how to manage acute mania, mixed, hypomanic episodes, depression, and continued maintenance.[9]

The agreed-upon primary mood stabilizing agents include lithium, divalproex, carbamazepine, and bilateral electroconvulsive therapy. The recommended adjunctives include thyroxine, clonazepam, lorazepam, and psychotherapy.[20] However, we do not have a clear guideline for treating refractory bipolar patients.

TREATMENT OF REFRACTORY BIPOLAR PATIENTS

Lamotrigine and gabapentin are two of the most recent anticonvulsants under investigation for their efficacy in treating refractory bipolar patients. Studies indicate that lamotrigine may be a useful antidepressant and that gabapentin may be beneficial for treating mania. Early studies on topiramate suggest that it may have some antimanic effects.

Lamotrigine

In a double-blind, placebo-controlled study, we evaluated the effect of 50-mg and 200-mg lamotrigine monotherapy in depressed bipolar patients. As demonstrated in *Figure 4*, the groups receiving lamotrigine did better than the placebo group, with those taking 200 mg doing the best.[21] Our data suggest that lamotrigine offers useful therapy for depressed bipolar

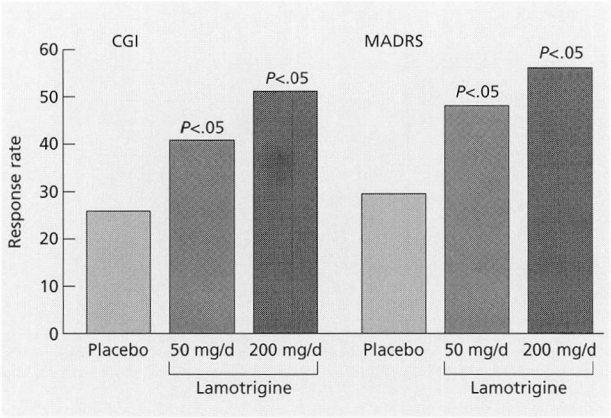

FIGURE 4. The response rate of depressive bipolar patients to monotherapy treatment with lamotrigine and placebo treatment in a double-blind, placebo-controlled study. Patients were evaluated on: Clinical Global Impression (CGI) and Montgomery-Asberg Depression Rating Scale (MADRS).

patients. However, more subjects in the 200-mg lamotrigine group switched from depression to mania than those taking placebo. Thus, while this study suggests that lamotrigine may be an effective antidepressant, the data shed doubt on its efficacy as a mood stabilizer.

An intriguing aspect of this study was the observation that side effects were reported by 92% of the placebo group, compared with only 76% of the lamotrigine patients. There was no difference between the control group and the experimental group in incidence of rash.

Dosing at Massachusetts General Hospital. Our dosing of lamotrigine differs from the recommended dosing in the *Physicians' Desk Reference* (PDR) (*Figure 5*).[22] Patients who are not taking divalproex or carbamazepine begin with a daily dose of 25 mg lamotrigine the first week and increase their dose weekly in increments of 25 mg until they reach 100 mg per day. Thereafter, we increase the dose from 25 to 50 mg on alternate weeks. We usually end up with a daily dose of 75 to 250 mg lamotrigine. Although the PDR recommends starting lamotrigine at 50 mg per day when used with an enzyme inducer,[22] we prefer starting with the lower dose because of the severe, potentially life-threatening rashes that have been associated with lamotrigine use. Potential risk factors for rashes include young age (lamotrigine is not approved for use in patients under 16 years), starting with a high dose, and fast rate of titration.[22]

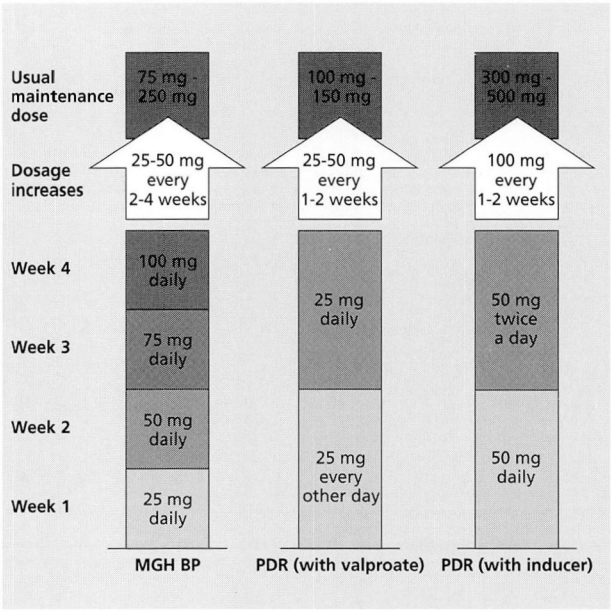

FIGURE 5. Lamotrigine dosing at Massachusetts General Hospital Bipolar Clinic (MGH BP), and the dosing suggested in the *Physicians' Desk Reference* (PDR).[22]

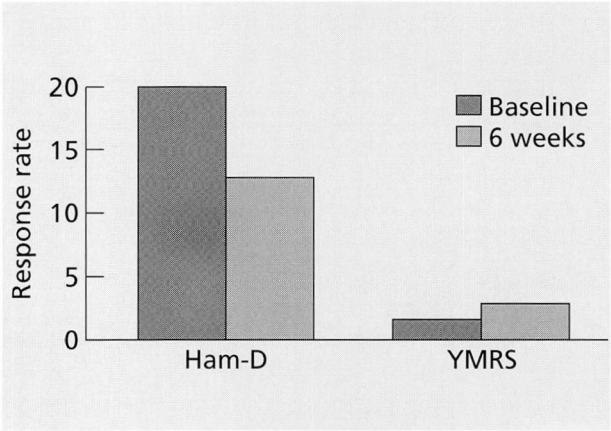

FIGURE 6. Gabapentin open treatment of refractory, depressed patients with bipolar disorder (N = 30). For 6 weeks, individuals received daily 1000 to 2000 mg gabapentin. HamD = Hamilton Depression scale; YMRS = Young Mania Rating Scale. After Young LT,[23] with permission.

Gabapentin

In an open trial, Young[23] gave gabapentin as adjunctive therapy to refractory patients suffering from bipolar depression. The participants received oral doses twice or three times a day, with the target dose between 1000 and 2000 mg. The mean dose was 1000 to 2000 mg.[23] After 6 weeks (*Figure* 6), the patients showed a significant decrease in Hamilton Depression Scale (HamD) scores but no clinically significant change in Young Mania Rating Scale (YMRS) scores. This suggests that gabapentin may be an effective treatment for mania in bipolar patients.

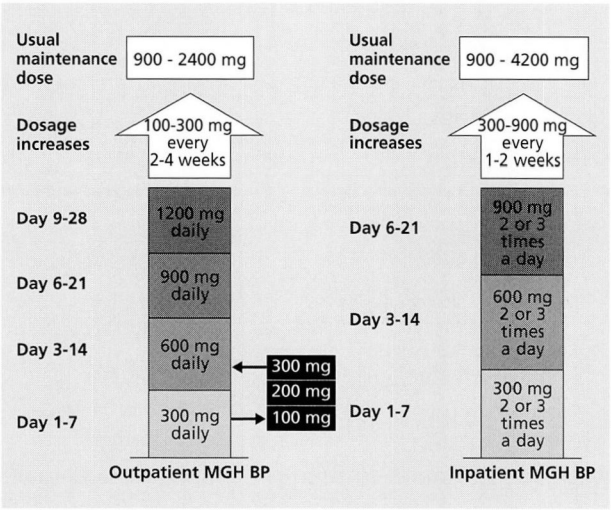

FIGURE 7. Gabapentin dosing of outpatients and inpatients at Massachusetts General Hospital Bipolar Clinic (MGH BP). qd = every day; bid = twice a day; tid = three times a day.

Dosing at Massachusetts General Hospital. We treat manic patients with gabapentin. Our goal in treating outpatients with gabapentin is usually improving their sleep patterns and reducing their agitation. Our inpatients are usually treatment-refractory manic patients, and we try to bring their agitation under control. We start outpatients on 300 mg per day; if a patient cannot tolerate 300 mg, we cut back to 100 mg per day and then slowly increase the dose to the recommended effective dose of 900 mg per day to 1800 mg per day (*Figure 7*).[24] Inpatients are treated more aggressively, starting with 300 mg two or three times a day. We increase the dose until we bring the agitation under control.

Topiramate

Open treatment of acute manic patients with topiramate did not change their depression score.[25] There was, however, some drop in the average mania score in individuals treated with doses up to 1600 mg per day.

Major side effects of topiramate are somnolence and fatigue.[26] In general, patients initially thrive on topiramate. Within 2 to 3 weeks, however, many

report severe fatigue and psychomotor retardation. Thus, using this drug can be challenging.

In conclusion, the recently available anticonvulsants lamotrigine and gabapentin seem to be useful in treating both depression and mania in some treatment-resistant patients. However, it is too early to predict whether either of them will be a good mood stabilizer.

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Panic disorder and social phobia: Current treatments and new strategies

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Panic disorder and social phobia are two common anxiety disorders that affect many adults in the United States today. It has been estimated that 3.5% of adults in the United States will suffer from panic disorder at some time in their lives,[1] and that 13% will experience social phobia.[1] Left untreated, the ultimate outcome of these pathologic reactions can be devastating: significant impairment can occur in several realms, including perceived physical and emotional deterioration, reduced productivity, increased absenteeism, onset of alcohol abuse, marital discord, and even suicide.

Treatment for panic disorder and social phobia can dramatically improve patient functioning and quality of life. A combination of psychotherapy and pharmacotherapy is most often used to control anxiety symptoms and enable patients to resume a normal routine and productive lifestyle. Until the 1980s, benzodiazepines were the pharmacologic agents of choice for anxiety disorders: they were considered highly effective and largely safe. As the associated cognitive impairment and abuse potential became apparent, however, scientists searched for newer agents with improved safety profiles.

In the last decade, several classes of compounds with anxiolytic efficacy without the risk for cognitive impairment, abuse, or dependence observed with benzodiazepines have been identified. The most promising of these agents are the selective serotonin reuptake inhibitors (SSRIs) and anticonvulsants. The roles for these compounds in panic disorder and social phobia are reviewed here, particularly in the historical context of benzodiazepine use and its inherent benefits and risks.

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PANIC DISORDER

Cost benefits of therapy

The benefit of successful treatment for panic disorder has been documented in an analysis of clinical status and health care utilization among patients before and after successful treatment for panic disorder. In Spain, Salvador-Carulla and coworkers[2] collected data on 61 patients with panic disorder from 12 months before diagnosis for comparison with data for 12 months after their treatment was initiated. In the year before therapy, the patients had lost more than 1,000 workdays; in the 12 months after diagnosis and during therapy, all were back at work, with only 190 sick days accumulated overall.

This substantial improvement in productivity translated into a significant financial benefit. Although direct health care costs due to medical care were about one-third greater in the year after diagnosis than in the 12 months before (per-patient costs of $478 versus $758, respectively), the indirect costs—eg, measures of lost productivity, employer costs—were almost 80% lower in the year after treatment (per-patient costs of $1,076 versus $228, respectively) resulting in an overall cost reduction associated with effective therapy for panic disorder. The substantial overall cost savings warrants a public health effort to properly diagnose and treat panic disorder.

TABLE 1
CHARACTERISTICS OF MAJOR HIGH-POTENCY BENZODIAZEPINES USED IN THE TREATMENT OF PANIC DISORDER AND SOCIAL PHOBIA

	Alprazolam	Clonazepam
Efficacy	Yes	Yes
Dose range	2–9 mg/day	1–4 mg/day
Dose frequency	3–4 times daily	1–2 times daily
Half-life	6–27 hours	18–50 hours

Treatment goals in panic disorder

The goals of therapy for panic disorder are well defined: prevention of panic attacks; reduction of anticipatory anxiety; elimination of phobic avoidance behavior; and control of common comorbid conditions. Meeting these goals often requires long-term intervention, since terminating treatment, particularly when done early in the course of the disease, results in a high relapse rate.[3] Continuous and long-term treatments are safe and the most effective approaches to panic disorder; therapy is the most reliable way to improve patients' quality of life.

Treatment for panic disorder is a multifaceted effort. Every patient should be educated about the causes and course of his or her condition, without stigmatizing the diagnosis. Cognitive-behavioral or other psychosocial therapies also can be instituted to teach patients skills for altering their maladaptive behavior. Pharmacotherapy—treatment with tricyclic antidepressants, benzodiazepines, monoamine oxidase inhibitors (MAOIs), SSRIs, and anticonvulsants—is used for the expeditious elimination of panic symptoms, and for effective maintenance of control over these symptoms.

Historical review of treatment for panic

In 1964, Klein[4] reported success in treating panic attacks with the tricyclic antidepressant imipramine. Imipramine eliminated panic attacks in a group of patients who had not responded to treatment with phenothiazines or sedative agents. Although this was a revolutionary observation at the time, the use of tricyclics—including clomipramine, desipramine, and nortriptyline, in addition to imipramine—was supplanted by the next generation of anxiolytic drugs, the benzodiazepines.

The benzodiazepines rapidly became standard therapy for panic disorder because they were highly effective and easy to use. Alprazolam and clonazepam are the benzodiazepines most commonly administered for panic disorder, and both have been proven to effectively control panic attacks (*Table 1*). Alprazolam is effective at higher doses and must be given more frequently than clonazepam, which can be administered only once or twice a day. The notable activity of clonazepam was documented recently by Rosenbaum and colleagues.[5] In a multicenter, parallel-group, placebo-controlled, fixed-dose trial, 413 patients with panic disorder were randomized to one of five daily doses of clonazepam (0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, and 4.0 mg) or placebo. Although the 0.5-mg clonazepam dose did not significantly reduce the number of panic attacks compared with placebo, daily doses of 1.0 mg or higher all provided equivalent efficacy and superiority to placebo in controlling panic symptoms.

Although long-term use of benzodiazepines in the treatment of panic disorder is generally effective and safe, there are two main concerns with their use. First, dose-dependent side effects such as somnolence, irritability, and ataxia may increase to the point where they detract from the patient's sense of well-being. In addition, although tolerance levels necessitating dose increases are unusual, dependence can be a concern with long-term benzodiazepine use.[5] Discontinuation of benzodiazepine therapy, therefore, must be approached as a slow, deliberate process in order to lessen the risk of rebound—the transient worsening of panic symptoms—and withdrawal symptoms. The occurrence of a withdrawal syndrome marked by symptoms ranging from irritability, headache, and tremor to delirium and even seizures is a function of several factors which include the duration of drug use, the characteristics of the specific drug, and the tapering schedule. Several studies have shown that a gradual discontinuation program and/or simultaneous cognitive-behavior therapy can increase the success rate and the ease of terminating benzodiazepine use.[6,7] This is an important benefit for the significant number of patients who, after long-term benzodiazepine use, have found it difficult to discontinue the drug.

Identification of newer agents

As it became clear that the tricyclic antidepressants and benzodiazepines had significant shortcomings in the long-term therapy for panic disorder, an

effort was made to identify effective agents with improved safety profiles and less risk for abuse. In this setting, the SSRIs have proven to be effective alternatives for the treatment of panic disorder. Although only paroxetine and sertraline have formal indications for management of this disorder,[8,9] fluoxetine and fluvoxamine also have been shown in open-label or double-blind, placebo-controlled trials to successfully improve panic symptoms.[10–14]

TABLE 2
ADVANTAGES AND DISADVANTAGES OF SSRI DRUGS IN THE TREATMENT OF PANIC DISORDER

Advantages	Disadvantages
Broad-spectrum efficacy	Slow onset
Abuse-free	Overstimulation
Beneficial for comorbid depression	Activation of sexual and gastrointestinal side effects
	Interaction with drugs metabolized by the cytochrome P450 isoenzyme system

Paroxetine and sertraline have both been shown to decrease the number of full- and limited-symptom panic attacks, to reduce the intensity of attacks, and to improve the quality of life in patients with panic disorder with and without agoraphobia,[15–18] without any risk for abuse or dependence (*Table 2*). The onset of action of SSRIs is relatively slow, requiring 6 to 12 weeks for full efficacy. In addition, a significant complication of SSRI use is agitation occurring early in the course of therapy, particularly with the use of high initial doses. This side effect can be very distressing to the patient, who may on occasion decide to discontinue treatment prematurely. Slow titration up to an effective dose may minimize the risk of this outcome but can also delay the time to full drug activity. Other potential side effects of SSRI therapy include somnolence, insomnia, constipation, nausea, diarrhea, sweating, and sexual difficulties, especially impaired orgasm. These reactions may lead to discontinuation.

With the side effects and difficulties associated with the use of benzodiazepines and antidepressants, there obviously was room for improvement in the form of another category of medication. Anticonvulsant agents were identified as a class of drugs with much to offer. First, there are a number of phenomenologic similarities between panic attacks and features of complex partial seizures, in that panic episodes and depersonalization can sometimes be seen in the latter. The GABA-ergic activity and antikindling effects of anticonvulsants might also provide some benefit in the treatment of panic attacks.

There is little formal experience with the use of anticonvulsant drugs in the treatment of panic disorder, but studies performed to date are suggestive of activity. Lum and colleagues[19] found that the intensity and duration of panic attacks in 12 patients with diagnosed panic disorder responded to treatment with valproate. Woodman and Noyes[20] reported results from a 6-week open clinical trial of valproate involving 12 patients with panic disorder. They noted marked improvement in 75% of patients; among 11 patients who elected to continue therapy, all showed sustained improvement at 6 months' follow-up. Although the numbers of subjects in these trials were small, there was a clear trend suggesting that anticonvulsant therapy is beneficial in the treatment of panic disorder.

Keck et al[21] examined the efficacy of valproate in panic disorder in an interesting prospective, open-label trial. They observed 16 patients treated with a 28-day regimen of valproate following lactate infusion to induce panic symptoms and compared the data with results derived from a subsequent lactate rechallenge. Of the 14 patients completing the trial, 71% experienced a > 50% reduction in the frequency of attacks, including 6 patients who had complete remissions. On lactate rechallenge, valproate blocked symptoms in 83% of individuals who had experienced symptoms on the initial infusion. These findings support the concept that valproate can meaningfully and effectively correct some of the underlying psychobiologic disturbances in panic disorder, possibly including increased GABA-ergic neurotransmission or antikindling activity.

Gabapentin is of clear theoretical relevance for the treatment of panic disorder, and the results of a recent controlled trial are currently undergoing analysis.

SOCIAL PHOBIA

Social phobia is defined as the pathologic fear of scrutiny by other people in social settings, particularly a marked and persistent fear of performance situations or social settings that are potentially embarrassing or humiliating. The fear causes disabling distress, leading to avoidance of the threatening setting. This relatively common anxiety disorder affects between 10% and 15% of the US population at some time in their life; similar rates have been observed in European countries as well.[1,22]

Generalized social phobia, wherein fears pervade almost all areas of interpersonal functioning, is the most common clinical manifestation of this diagnosis, as well as the most disabling. Performance or nongeneralized social phobia is less commonly seen in clinical settings and its pharmacotherapy is less well understood.

Treatment goals in social phobia

As in panic disorder, the treatment goals for social phobia center on eliminating episodes of anxiety and returning the patient to a "normal" level of daily functioning and interpersonal relations. Two forms of treatment have been found to be effective in meeting these goals. Psychosocial therapies involving exposure, cognitive restructuring, and cultivation of social skills provide a solid basis for relearning behavioral responses. Pharmacotherapy is also useful for treating social phobia, and the range of agents used in the treatment of this disorder have included beta-blockers, MAOIs, benzodiazepines, tricyclic antidepressants, and SSRIs. One study suggests that the best outcome is achieved with a combination of psychotherapy plus pharmacotherapy.[23]

Among the original pharmacologic agents examined for the treatment of social phobia, beta-blockers have been found to show no efficacy[24] for generalized social phobia. The MAOIs, although effective, are difficult drugs to use, requiring dietary restrictions and carrying the risk of significant side effects, such as hypertensive crisis and intracranial bleeding.[24,25] The selective, reversible inhibitor of MAO-A, moclobemide, is of some benefit at daily doses of 600 mg,[26] although another major trial showed no effect for the drug.[27] The benzodiazepine drug, clonazepam was shown to be highly effective in predominantly generalized social phobia.[28]

The next section will focus on further effective and practical drug-treatment options for social phobia. These include the SSRIs and, as of recently, the anticonvulsant agent gabapentin.

DRUG OPTIONS FOR THE TREATMENT OF SOCIAL PHOBIA

SSRIs

There are both controlled and anecdotal reports describing the efficacy of the SSRIs in the treatment of social phobia.[29–35] The most extensively studied SSRI and the first of this class to be approved for use in this indication is paroxetine.[35,36]

In a randomized, double-blind, multicenter study, Stein and coworkers[36] compared the efficacy of paroxetine versus placebo in the treatment of 187 patients with generalized social phobia. At the end of the 12-week trial, 50 (55%) of 91 persons taking paroxetine were significantly improved according to the Clinical Global Impression (CGI) Global Improvement Item, compared with 22 (23.9%) of 92 patients receiving placebo ($P = .001$). Mean scores on the Liebowitz Social Anxiety Scale (LSAS) fell by 39.1% and 17.4% in the paroxetine and placebo groups, respectively ($P < .001$). This representative study established the efficacy of paroxetine in reducing the symptoms and disability of social phobia.

Similarly, positive results have been reported with sertraline[37] and fluvoxamine.[38] No placebo-controlled experience with fluoxetine in the treatment of social phobia has been reported to date.

Gabapentin: A novel anticonvulsant agent

Gabapentin is the first anticonvulsant agent to be tested for the treatment of social phobia in a double-blind, randomized, placebo-controlled study. In this 14-week trial, 60 patients > 18 years of age with a clinical diagnosis of social phobia were randomly assigned to treatment with 900 to 3,600 mg/day of gabapentin, or placebo, as described in the report by Pande et al (1998).[39] All patients had LSAS scores of > 50 and Hamilton Depression Scale (HamD) scores of < 2 on Item 1, were not current alcohol or

substance abusers, and provided written informed consent.

Baseline measures of LSAS, Brief Social Phobia Scale (BSPS), Marks' Fear Questionnaire (MFQ), Social Phobia Inventory (SPIN), and CGI were recorded and followed at regular intervals during treatment (1, 2, 3, 4, 6, 8, 10, 12, and 14 weeks). Vital signs and laboratory measures were assessed, and adverse event histories were recorded at each visit.

TABLE 3
ADVERSE EVENTS ASSOCIATED WITH GABAPENTIN THERAPY IN THE TREATMENT OF SOCIAL PHOBIA (INCIDENCE > 5%)

Adverse Event	No. Pts (%) Gabapentin (n=34)	No. Pts (%) Placebo (n=35)	Fisher's Exact Test (*P*)
Dizziness	8 (24)	2 (6)	.05
Somnolence	7 (21)	3 (9)	.19
Dry mouth	4 (12)	0 (0)	.05
Flatulence	3 (9)	0 (0)	.11
Decreased libido	3 (9)	0 (0)	.11

At the last follow-up visit, the response rate, based on CGI scores, was greater in the gabapentin group compared with the placebo group (39% vs 19%, respectively; $P < .05$). The effect size—which is a measure of the magnitude of the drug treatment effect—approached 0.7 on the BSPS and CGI-I. (A score of 0.5 is considered a moderate treatment effect, making 0.7 a relatively strong measure of drug impact.) A more modest, but still meaningful, effect size of 0.4 was observed on the LSAS.

Side effects of gabapentin therapy were moderate and did not impair the safety or tolerability of treatment (*Table 3*). Dizziness (24% vs 6% with gabapentin and placebo, respectively) and dry mouth (12% vs 0%, respectively) were the only side effects that occurred with statistically significant greater frequency with gabapentin compared with placebo therapy.

The results of this trial indicate that gabapentin is a well-tolerated, effective alternative for the treatment of social phobia, with a moderate to good effect size on clinical measures of anxiety symptomatology. Higher baseline scores of severity on the SPIN scale, as well as more severe physiologic symptoms and agoraphobic avoidance behavior as determined by the MFQ scale, predicted better response to gabapentin therapy. This is especially important because phobic avoidance is one of the more difficult-to-treat aspects of social phobia. Gabapentin is a promising new approach to the pharmacotherapy of social phobia without many of the complications associated with SSRI and benzodiazepine treatment.

SUMMARY

Panic disorder and social phobia are among the most disabling of the anxiety disorders. The emotional cost to the patient suffering from these diagnoses is exceeded only by the very real economic costs to the community because of reduced productivity, lost workdays, and increased health care costs for associated physical complaints. It is imperative, therefore, that the medical community focus on the accurate diagnosis and effective treatment of these potentially devastating conditions.

Pharmacologic treatments for panic disorder and social phobia have been available since the early 1960s. The limited efficacy and significant side effects of the early medications, however, led to a search for new treatment options. For many years, the benzodiazepines were the principal first-line therapy for treatment of these illnesses. Yet, their potential for cognitive impairment, physiological dependence, abuse, and withdrawal phenomena warranted a continued search for newer agents with an improved safety profile. In the last 10 years, several treatments have been identified that may fill this need.

Controlled trials and/or anecdotal reports have shown SSRIs and anticonvulsants to be effective treatments for the symptoms of panic disorder and social phobia. However, although SSRIs are emerging as a leading treatment for generalized social phobia, it is not at all clear whether they can benefit nongeneralized social phobia. Their side-effect profile, while a marked improvement over earlier antidepressant drugs, still can cause significant dis-

comfort. The anticonvulsants are now emerging as a very important group of drugs in the anxiety disorders, with gabapentin having been the most extensively studied in social phobia.

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Panel discussions

HAROLD H. MORRIS III, MD, EDWARD C. COVINGTON, MD, GARY S. SACHS, MD, AND JONATHAN R.T. DAVIDSON, MD

Question: Gabapentin comes across as quite a safe drug. Are there any administration guidelines that need to be considered when prescribing this agent?

Dr. Morris: Gabapentin is a safe compound, but there are some precautions that must be observed. Gabapentin is a renally excreted drug, and any drug that must be cleared depends on the adequate maintenance of physiologic systems. As one ages, renal clearance decreases, and as a result levels of gabapentin may rise. For practical purposes, however, as long as BUN and creatinine levels remain normal, it will not be necessary to alter gabapentin dosages.

Question: Can you elaborate on the cognitive effects of topiramate therapy?

Dr. Morris: The cognitive toxicity of topiramate is highly idiosyncratic: there is no way to predict which patients will be affected by it. When it does occur, it may become evident with doses as low as 50 to 100 mg. But some people are extremely tolerant, and can safely receive up to 1800 mg/day of topiramate without any problem. Cognitive toxicity may also be insidious; patients themselves may not recognize its onset, and family and friends may recognize the symptoms first. The cognitive side effects respond to dose reductions, potentially even disappearing if the dose is reduced sufficiently.

Question: I have heard of a similar syndrome of insidious dementia occurring with valproate. Is this a documented effect?

Dr. Morris: Yes, but rather than a simple dementia, the true profile of this adverse reaction includes a parkinsonian syndrome, as well as a loss in cognition and slowed thinking. This picture also is reversible on discontinuation of therapy.

Question: Are there any guidelines for determining which anticonvulsant is best to use for different sources of pain?

Dr. Covington: At this point, I consider gabapentin the first-choice agent for pain of most origins. It has few drug-drug interactions because it does not metabolize and does not undergo autoinduction, and, because of its simple transport and excretion, it is not necessary to monitor liver and hematologic indices. One of its most important advantages is its wide spectrum of activity. Gabapentin is a very safe agent, with few side effects, making it a logical choice for the empiric treatment of idiopathic pain.

Question: Is clonazepam the only benzodiazepine effective in the treatment of neuropathic pain?

Dr. Covington: Yes, although the reasons for this unique activity are unknown. Pain relief has not been observed with any of the other benzodiazepines, including diazepam, lorazepam, or alprazolam.

The main drawback of clonazepam in the treatment of neuropathic pain is its risk for dependence. I prefer to use a drug with no addiction potential whenever I can, rather than chance substance abuse. Therefore, I usually reserve clonazepam therapy for recalcitrant pain states.

Question: In my experience, gabapentin ameliorates the restless leg syndrome at doses as low as 100 mg per night. Is it also effective for pain relief at unexpectedly low doses?

Dr. Covington: Many pain patients respond to treatment with 900 mg/day gabapentin, which is a relatively low dose. Some patients, however, taking 300 mg tid gabapentin will regress between doses, experiencing renewal of pain before the next dose is scheduled. Yet in drug-naive patients, especially the elderly, it is important to begin treatment at a low dose and titrate up cautiously. During this titration

period, the initial response that occurs shortly after drug intake may wear off before it is time to take the next dose. It is important that the physician, as well as the patient, be aware of this potential lag and know that it will resolve with further drug titration.

Question: What is the protocol for managing benzodiazepine withdrawal with anticonvulsant drug therapy?

Dr. Covington: Benzodiazepine withdrawal therapy is not a science and must be individualized. Although there are equivalency tables meant to enable slow conversion away from benzodiazepine by adding increasing doses (to equal effect) of the therapeutic anticonvulsant, there are several problems with this approach. First, many patients are not aware of exactly what dose of benzodiazepine they have been ingesting, and so it is impossible to equivalently convert. Second, some patients forget how much drug they have ingested. Lastly, some patients simply are not truthful about how much they have been taking.

Therefore, I find it most expeditious to simply discontinue the benzodiazepine immediately and prescribe in its place 600 mg of gabapentin. The gabapentin dose is then repeated every 4 (to 6) hours, even dosing in the middle of the night if necessary in the early stages of transition. Within a week, I try to reduce the dosing period to q6h, then to 400 mg q6h, with continuing reductions until discontinuation is possible. All along I follow the patient with tendon taps, pulse measurements, and other objective evaluations.

It is difficult to predict an optimal anticonvulsant dose or the duration of withdrawal therapy. No reliable response prediction parameters have been recognized. Instead, the anticonvulsant dose is titrated upward and back downward based on autonomic signs and hyperreflexic responses indicative of a withdrawal reaction.

Question: Do the different benzodiazepines yield unique response and withdrawal patterns to gabapentin use?

Dr. Covington: No. Withdrawal from any of the benzodiazepines appears to follow a similar pattern, and all respond to gabapentin therapy.

Question: Dr. Sachs, your lamotrigine vs. placebo slide (*Figure 4, page SI-35*) shows a placebo response rate of 25% to 30%. In epilepsy, placebo rates are around 8% to 10%, and if they are higher, we worry about the validity of the study. Can you comment on this?

Dr. Sachs: Placebo response rates in bipolar depression studies are just over 25%. The rate in the study I showed is actually much lower than in almost any other study you are going to see in psychiatry.

Typically, placebo rates have been around 30%. In anxiety disorder studies, it is hard to show a benefit for any drug, not because the drugs are not working, but because the placebo responses are very high. So, 25% is not out of line for psychiatry.

Question: My question is related to your inpatient treatment of acute mania with gabapentin. Why are you using such low doses of gabapentin when you have someone completely controlled in the hospital? Why don't you give them 3600 mg on day one?

Dr. Sachs: I think it is mainly because we don't know that we can do that. We know that we can do that with divalproex, but we do not know what will happen with gabapentin.

There are patients who respond beautifully to 300 mg/day. They sleep; they are sedated the next day. You wish you knew who was going to have which type of response. But we are doing this over a period of days.

If somebody would do a study and let us know that we could start at 3600 mg or that starting at 300 mg and stepping up is just as useful, then we would be able to do it. But right now we do not have the data.

Question: Why doesn't psychiatry come up with mood stabilizers that are not anticonvulsants, that are not antihypertensives, like calcium channel blockers? The medications we use are clearly potent, and yet we are beginning to treat more and more bipolar patients with them, especially children. Why are we not looking for membrane stabilizers that do not have some of these more toxic side effects?

Dr. Sachs: Omega-3 fatty acids may be an example of that. But often, we are reinventing the wheel for the most part. Once we see what seems to work, we do variations of it until we have another serendipitous finding.

It is very hard to know what is likely to work. As we are beginning to get classes of drugs that actually can target specific mechanisms, such as the phosphoinositol cycle, it becomes really interesting. There are new classes of drugs on the way; they are just not yet studied. So, we are looking; we just do not have them yet.

Question: I understand your rationale as far as lamotrigine, but given the neurologists' experience with this, why not step up the rate?

Dr. Sachs: In Germany they have started at 200 mg and their rash rate is 40%. To me, that is a good reason not to go faster. We start at 25. Rash usually happens within 6 to 8 weeks, and you do have to worry about it later. There are serious late-occurring rashes; it is just that they are less common. Most of them have occurred in the 6- to 8-week range.

Question: Dr. Davidson, in your trial, patients received gabapentin for 14 weeks. Is this the anticipated duration of therapy in a nontrial setting?

Dr. Davidson: No, in clinical management 14 weeks is an inadequate treatment period for social phobia. It is more likely that gabapentin treatment will continue for at least 12 months. Earlier discontinuation is associated with a high likelihood of relapse.

In these trials relapse rates ranged from a low of 20% to a maximum rate of about 100%. The latter figure resulted from discontinuation of maclobamide, clonazepam termination led to relapse in 20%, brofaromine in about 70%, and paroxetine in approximately 60% of patients after 6 to 12 months of treatment.

Question: In using gabapentin, I have observed excellent compliance among patients, not simply because it is an easy medicine to take, but also because it improves the patient's sense of well-being as well as his or her cognitive function, especially the sense of objectivity. People begin to sound more mature and self-assured. Are these established features of gabapentin therapy?

Dr. Davidson: Yes, patients receiving gabapentin experience not only improvement in clinical symptoms but also greater insight and mature thinking. One of the reasons gabapentin has been so well-received as treatment of social phobia is for exactly that reason. Gabapentin has a disinhibiting effect. Social phobia, being a distinct pathologic inhibition and fear of expressing opinions, benefits greatly from this particular feature of gabapentin.