Can Anticonvulsants Help Patients With Anxiety Disorders?

February 01, 2009 | Anxiety [1], Bipolar Disorder [2], Comorbidity In Psychiatry [3], Generalized Anxiety [4], Major Depressive Disorder [5], Addiction [6]
By Marco Mula, MD, PhD [7]

The rationale for the use of anticonvulsants in anxiety disorders is supported by neurobiological underpinnings that make these compounds a likely alternative for short-term treatment.

In This Special Report:
The Intricacies of Diagnosis and Treatment, by Thomas L. Schwartz, MD

Strategies for Assessing and Treating Comorbid Panic and Generalized Anxiety Disorder, by Kristalyn Salters-Pedneault, PhD
Can Anticonvulsants Help Patients With Anxiety Disorders? by Marco Mula, MD, PhD
SSRIs as Antihypertensives in Patients With Autonomic Panic Disorder, by Sean Hood, MBBS, MSc
Achieving Remission in Generalized Anxiety Disorder, by Laura A. Mandos, PharmD, Jennifer A. Reinhold, PharmD, and Karl Rickels, MD

Anxiety disorders are chronic conditions that follow a relapsing/remitting course. The evidence to support this view comes primarily from cross-sectional and retrospective assessments of duration of illness and, in part, from prospective studies. The waxing and waning nature of panic disorder and generalized anxiety disorder (GAD), for example, has been clearly demonstrated. Much less information is available about the course of illness of social phobia. However, both community studies and patient samples suggest an age of onset of social phobia in mid to late teens with a chronicity that is equal to or greater than that of panic disorder. Nevertheless, this recognition has not reshaped our basic treatment approach, which focuses almost entirely on the acute control of symptoms and only secondarily acknowledges relapse prevention. In addition, the natural history of anxiety disorders is frequently complicated by Axis I and Axis II comorbidity that seems to be significantly higher among patients who seek treatment than in persons in the community who are not in treatment. In fact, it has been estimated that 73% of patients with panic disorder had other comorbid conditions that ranged from major depression to substance abuse until the onset of the Axis II disorders, mostly cluster C type 1 to 2. It is, therefore, evident that any long-term anxiolytic treatment strategy must take account of these high rates of comorbidity that appear to develop during the longitudinal phase of the anxiety disorder.
A variety of drug classes have been shown to be effective in treating anxiety disorders. SSRIs are the current gold standard for anxiety disorders. Effective in about 50% to 60% of patients, serotonin noradrenalin reuptake inhibitors are now considered the gold standard specifically for panic disorder and GAD. Benzodiazepines have a rapid onset of action, but their long-term use may lead to complications, such as abuse liability, dependence, and withdrawal risk if the dosage is not tapered properly. Moreover, in some patients, benzodiazepines may cause sedative effects and cognitive deficits that significantly affect quality of life and social functioning. The basis for the use of anticonvulsant drugs in treating anxiety disorders can be found in the main cerebral structures involved in fear circuits. Although numerous brain regions are likely to be involved, the amygdala and the hippocampus play a key role. The amygdala is important in experiencing fear and its autonomic and endocrine response through the output to the hypothalamus, while the output to periaqueductal gray matter is mainly implicated in avoidance behavior, which is also typical of fear response. In addition, the hippocampus is important in the re-experiencing of fear and the cognitive aspects of fear and anxiety. The reduction of an excessive output from these neurons may theoretically diminish anxiety symptoms. In fact, anticonvulsant drugs exert their antiseizure activity by decreasing the excessive outbursts from epileptic neurons. Therefore, these drugs could reduce symptoms of anxiety by decreasing neuronal activation within fear circuits. Unlike other drug classes, anticonvulsants are not usually categorized according to their mechanisms of action or chemical structure. This is because their actions are not completely understood at the molecular level, and current knowledge indicates that almost all antiepileptic drugs have more than one mechanism of action (Table 1). Among all known mechanisms, the potentiation of g-aminobutyric acid (GABA)-ergic inhibition and the modulation of voltage-activated calcium channels may be most responsible for the pathophysiology
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GABA is the principal inhibitory neurotransmitter and, along with serotonin and noradrenalin, is one of several neurotransmitters that appear to be involved in the pathogenesis of anxiety. Drugs that stimulate GABA receptors, such as benzodiazepines, have both anxiolytic and antiseizure effects via GABA-mediated reduction of neuronal excitability. The GABA receptor subtype regulates excitability and rapid changes in fear arousal, such as anxiety, panic, and acute stress response. However, the sedative hypnotic effect of benzodiazepines is the result of an allosteric-positive modulation of GABA receptors that contain the alpha-1 subunit. The anxiolytic effect seems to be related to an allosteric modulation of receptors that contain the alpha-2 subunit. It is evident that GABA modulation is a determinant for both anxiety and seizures: in fact, GABA antagonists produce convulsions in animals. A study using positron emission tomography showed that patients with panic disorder have a decrease in GABA receptor binding. Not all classic GABA-ergic anticonvulsants exert helpful psychoactive properties. Although their pharmacological profile suggests anxiolytic properties, barbiturates, vigabatrin, and topiramate may have treatment-emergent psychiatric adverse effects. Agitation and hyperactivity have been

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**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Calcium channel block (type)</th>
<th>GABA potentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturate</td>
<td>NK</td>
<td>+ (A)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>NA</td>
<td>++ (A)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+ (L)</td>
<td>NK</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>++ (T)</td>
<td>NA</td>
</tr>
<tr>
<td>Felbamate</td>
<td>+ (L)</td>
<td>+ (A)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>++ (N, P/Q)</td>
<td>NK</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>+ (N, P/Q, R)</td>
<td>+</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+ (N)</td>
<td>NK</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>+ (N, P)</td>
<td>NK</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>NK</td>
<td>NA</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>++ (N, P/Q)</td>
<td>NA</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>NA</td>
<td>++</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+ (L)</td>
<td>+ (A)</td>
</tr>
<tr>
<td>Valproate</td>
<td>NK</td>
<td>+</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>NA</td>
<td>++</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>++ (N, P, T)</td>
<td>NK</td>
</tr>
</tbody>
</table>

GABA, γ-aminobutyric acid; ++, primary action; +, secondary action; NA, no activity; NK, controversial findings; A, GABA potentiation through GABA receptors.
described with barbiturates, especially in children, and it is well documented in the neurological literature that both vigabatrin and topiramate are associated with depression and psychoses. This may be a consequence of GABA-ergic neurotransmission. The emerging understanding of different roles for phasic or synaptic inhibition and tonic inhibition mediated by different subpopulations of GABA<sub>A</sub> receptors may lead to targeted compounds for anxiety disorders.

**Calcium channel blockers**

Calcium channel blockers represent another class of molecules that can be of relevance in anxiety. They have been shown to be of value in ameliorating symptoms in animal models of anxiety. In general terms, calcium channels can be categorized according to their biophysical and pharmacological properties in 2 main subfamilies: high-voltage–activated and low-voltage–activated channels. The former are differentiated into different subtypes: l-type (generating a long-lasting current); and N-, P/Q-, and R-types (expressed in nerve terminals and responsible for the calcium entry that triggers neurotransmitter release). On the other hand, low-voltage–activated calcium channels (T-type) generate transient currents, have a somatodendritic localization, and are critical to pacemaker activity and some patterns of burst firing.

Among the different subtypes, it seems that high-voltage calcium channels, in particular the N- and P/Q-types, may represent interesting molecular targets for antianxiety compounds because they regulate neurotransmitter release during synaptic neurotransmission, especially excitatory neurotransmission. The alpha-2-delta is a particular subunit of these channels, and it has been hypothesized that its modulation can be of value in controlling anxiety symptoms. In the case of gabapentin and pregabalin, N- and P/Q-type channels represent the main molecular target—in particular the alpha-2-delta subunit, type 1 and type 2. It has been suggested that the binding to this calcium channel subunit causes a channel conformational change, which lowers calcium influx and neuron depolarization and, therefore, firing. It also has been suggested that the expression of the alpha-2-delta subunit differs in different cell types in response to different conditions. For example, in chronic neuropathic pain, alpha-2-delta subunits may be up-regulated, which explains, at least in part, the efficacy of gabapentin and pregabalin in such a condition. It remains to be determined whether such plastic changes are also present in anxiety disorders.

Despite numerous open studies and reports, most publications have several methodological limitations, including inadequate sample size; lack of placebo control; use of outcome measures, such as the clinical global impression scales; and lack of controlling for patient variables, such as comorbidity, diagnostic subtype, and concomitant medications. These factors may help explain why anticonvulsants have yielded inconsistent results in the treatment of anxiety disorders.

**Generalized anxiety disorder**

The strongest evidence is for pregabalin in patients with GAD with and without comorbidity (Table 2). Pregabalin has been shown to be effective at high dosages (300 to 600 mg/d) in a number of controlled studies compared with benzodiazepines and venlafaxine. Recent data support the efficacy of pregabalin in the long-term treatment and in the amelioration of comorbid depressive symptoms.

Regarding other anticonvulsant drugs, tiagabine is the only other compound being investigated for GAD. This agent has shown promise in an open study. However, controlled data from 260 patients showed no significant difference from placebo in responder rates measured with the Hamilton Anxiety Scale.

**Social anxiety disorder**

Controlled studies show interesting results for pregabalin (600 mg/d) and gabapentin (900 to 3600 mg/d). Both drugs share the same mechanisms of action, namely the modulation of N- and P/Q-type voltage-dependent calcium channels.

Among other anticonvulsant drugs, valproate and topiramate have been shown to ameliorate phobic symptoms in small open studies involving 17 and 23 patients, respectively. Further controlled studies are warranted to reach definitive conclusions.

Data on levetiracetam are not conclusive either. An open-label, flexible-dose study in 20 patients showed a clinically significant reduction in anxiety and phobic symptoms. However, results of a controlled study comprising 16 subjects were clearly negative, although some methodological limitations such as the small sample size make it impossible to get definitive evidence about this anticonvulsant for social phobia. Further investigations are needed.
Panic disorder
Although a number of anticonvulsant drugs have been used for panic disorder, conclusive data are not available. The majority of studies have been uncontrolled and have had small sample sizes. The results for gabapentin have been somewhat mixed, although post hoc analyses of a controlled study suggest that gabapentin (600 to 3600 mg/d) may be useful in patients with moderate to severe panic disorder.20
There are no more than anecdotal reports for vigabatrin, tiagabine, and oxcarbazepine. The literature is inconclusive for carbamazepine. Although an open study suggested a possible antipanic effect, the only controlled study conducted in a limited sample of 14 patients showed no effect.21 Theoretically, data on valproate may be more interesting and promising, although currently they are still limited to open studies.9-11

Posttraumatic stress disorder
At present, controlled studies of anticonvulsants involve lamotrigine and valproate.22,23 In one study, lamotrigine was associated with a significant diminution in the re-experiencing and avoidance/numbing symptoms relative to placebo.22 Unfortunately, only 10 patients in that study were followed and the dosage range was quite large (25 to 500 mg).22 These factors make any useful measure of effect size impossible.
Open studies of valproate for the treatment of posttraumatic stress disorder (PTSD) were initially promising, but a randomized, double-blind, placebo-controlled trial showed that the response to valproate monotherapy in 85 older male combat veterans was no different from that with placebo.9-11 Further studies are needed to determine the efficacy of monotherapy in women and the possible effectiveness of valproate as augmentation therapy.
Among other anticonvulsants, data are limited to open studies, which suggest some improvement in hyperarousal symptoms with carbamazepine, phenytoin, topiramate, and levetiracetam.9-11 Nonetheless, these are uncontrolled data that may deserve further investigations without any clear indication at the moment.

Obcessive-compulsive disorder
Among all anticonvulsant drugs, data on topiramate, from open studies, are the most compelling.9-11 Lamotrigine has been shown to be ineffective, while information on carbamazepine is limited to case reports.9-11

Who can benefit?
We are still far from straightforward guidelines on the use of anticonvulsants in patients with anxiety disorders. Apart from the direct comparison between pregabalin and venlafaxine for GAD, there are no head-to-head comparisons with first-line agents (ie, antidepressant drugs) for the long-term treatment of anxiety symptoms. Furthermore, there are no data about which clinical subgroups may preferentially respond to these drugs. Recent data on pregabalin suggest some utility in GAD with comorbid depression.

We can speculate that patients with comorbid bipolar disorders may benefit from a mood stabilizer with anxiolytic properties. In this setting, lamotrigine and valproate may represent valuable options, although evidence on these 2 compounds in treating anxiety disorders per se is weak. Gabapentin has not been shown to have strong mood-stabilizing properties and there are no data for pregabalin. Their use in patients with bipolar disorders and comorbid anxiety disorders seems premature.

Patients with anxiety disorders, obesity, and comorbid eating disorders (eg, binge-eating disorder, bulimia) may benefit from treatment with topiramate, although promising results are still confined to obsessive-compulsive disorder and PTSD.

Conclusions
The rationale for the use of anticonvulsants in anxiety disorders is supported by neurobiological underpinnings that make these compounds a likely alternative for short-term treatment in patients who do not respond to benzodiazepines or who have a contraindication (an addiction disorder, respiratory problems, or who are at risk for falls). However, data are limited, and current criteria for levels of evidence and lines of treatment recommendations suggest strong evidence only for pregabalin in patients with GAD with or without comorbidity (Table 2).

Pregabalin and gabapentin have been shown to be promising in social phobia. Data about gabapentin in panic disorder are somewhat mixed; they suggest a possible role only in patients who are moderately to severely affected. In any case, these compounds must still be considered second- or even third-line treatment.

Further studies are needed on the neurobiology of anxiety disorders and neuropharmacology of anticonvulsant drugs to develop pharmacological treatment strategies that target symptom patterns and patients’ needs.

Drugs Mentioned in This Article
Carbamazepine (Carbatrol, Tegretol, others)
Ethosuximide (Zarontin)
Felbamate (Felbatol)
Gabapentin (Neurontin)
Lamotrigine (Lamictal)
Levetiracetam (Keppra)
Oxcarbazepine (Trileptal)
Phenyoitn (Dilantin)
Pregabalin (Lyrica)
Tiagabine (Gabitril)
Topiramate (Topamax)
Valproate/valproic acid (Depakote, others)
Venlafaxine (Effexor)
Vigabatrin (Vigabatrine)
Zonisamide (Zonegran)

6. Malizia AL, Cunningham VJ, Bell CJ, et al. Decreased brain GABA(A)-benzodiazepine receptor
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