Anticonvulsants in Anxiety Disorders

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Abstract: The psychotropic use of anticonvulsants is an active area of research, with several case reports, case series and open trials suggesting their potential efficacy in various disorders. The strongest evidence, however, is from controlled studies. It supports the use of lamotrigine in posttraumatic stress disorder (PTSD); gabapentin in social phobia; pregabalin in social phobia, generalized anxiety disorder (GAD) and GAD with comorbidity; and valproic acid in panic disorder.

Although the anticonvulsants seem to be promising treatments for anxiety disorders, it is unclear at this point whether their place will be as first-line agents, as augmenting strategies, or as medications used in cases of treatment resistance or nonresponse to traditional pharmacotherapy.

Key Words: anxiety disorders, novel treatments, pharmacotherapy, anticonvulsants

Pharmacologic treatments for anxiety disorders have been evolving rapidly. Various drug groups have been shown to be effective, with selective serotonin reuptake inhibitors (SSRIs) being the current gold standard. Despite such widespread use, however, SSRIs can be associated with significant side-effects and are only effective in approximately 50 per cent to 60 per cent of patients. There is therefore a clinical need for alternative medication treatments, used either as monotherapy or as an augmentation strategy.

Anticonvulsants have been widely used in the treatment of mood disorders and have become first-line treatments for bipolar disorder (BD). The successful use of anticonvulsants in mood disorders has led clinicians and researchers to investigate their potential efficacy in other psychiatric disorders—particularly, anxiety disorders.

This article reviews the small but emerging literature on the use of anticonvulsants in anxiety disorders. Each anticonvulsant is reviewed according to the disorders in which it has been studied.

Lamotrigine

Lamotrigine is used as either an adjunct or monotherapy agent for epilepsy. It is thought to produce antiseizure effects by its action on voltage-sensitive sodium channels and subsequent inhibition of the release of glutamate and aspartate.

Posttraumatic Stress Disorder (PTSD)

In a placebo-controlled trial conducted by Hertzberg and colleagues (1), 14 patients with PTSD received lamotrigine or placebo for up to 10 weeks; dosages were up to 500 mg daily. Lamotrigine was found to be better than placebo on measures of intrusive thoughts and avoidance or numbing symptoms. Of those receiving lamotrigine, 50 per cent were classified as lamotrigine responders, compared with 25 per cent in the placebo group.

Topiramate

Topiramate is used adjunctively or as monotherapy in epilepsy patients. Topiramate appears to have several mechanisms of action. It has been shown to enhance the activity of gamma-aminobutyric acid (GABA) at nonbenzodiazepine sites (a GABA-A receptor subtype) and to inhibit glutamate via alpha AMP/kainate subreceptors. It appears to block voltage-gated sodium channels. It is also a weak inhibitor of carbonic anhydrase isoenzymes II and IV.

PTSD

Berlant and colleagues conducted an open-label trial of topiramate, used either as monotherapy or as adjunctive treatment, in 35 PTSD patients (2). Full response was achieved with a mean dosage of 43 mg daily in the monotherapy group and 97 mg daily in the adjunctive treatment group. Topiramate was found to reduce...
nightmares, intrusions and flashbacks in 80 per cent of the patients. After four weeks of treatment, 82 per cent of the patients no longer met criteria for PTSD.

Social Phobia (SP)
Van Ameringen and others conducted a 17-week open-label trial of 17 patients to evaluate the effectiveness of topiramate in treating SP (3). Dosages started at 25 mg daily and were titrated to 100 mg daily by week three, with a maximum dosage of 400 mg daily at week nine. In the intent-to-treat (ITT) sample, 9/17 were responders according to the Clinical Global Impression-Improvement Scale (CGI-I). In addition, a significant improvement from baseline to endpoint was found on the Liebowitz Social Anxiety Scale (LSAS).

Gabapentin
Gabapentin is an anticonvulsant that increases the release of nonsynaptic GABA from the glial cells, thereby decreasing neuronal overexcitability (4).

Social Phobia
In a 14-week randomized, double-blind, placebo-controlled study of gabapentin, 69 SP patients were treated with dosages ranging from 900 mg daily to 3,600 mg daily (5). The gabapentin group demonstrated significantly more reduction in SP symptoms than did the placebo group.

Panic Disorder (PD)
Successful treatment of PD with gabapentin has been documented in case reports (6) and in an eight-week double-blind, placebo-controlled study of 103 patients receiving dosages ranging from 600 to 3,600 mg daily (7). Pande and colleagues reported a nonsignificant difference in symptom severity between the treatment and placebo groups. However, a significant improvement was found in a severely ill subsample with PD.

PTSD
Brannon and colleagues documented a case report wherein 1,200 mg daily of gabapentin was found to successfully reduce anxiety and the frequency of nightmares in a patient diagnosed with PTSD (8). Similar results were found in a study of 30 PTSD patients who were treated with gabapentin as an adjunctive medication (9). It was found that 77 per cent of these patients demonstrated moderate or marked improvements in sleep duration and nightmares.

Generalized Anxiety Disorder (GAD)
Improvements in anxiety and arousal symptoms were noted in two case reports of GAD treated with gabapentin (6).

Obsessive–Compulsive Disorder (OCD)
Cora-Locatelli and colleagues reported the use of adjunctive gabapentin to treat OCD in five patients who were partial responders to fluoxetine (10). All patients in the six-week trial demonstrated improvements in anxiety, obsessive–compulsive symptoms, sleep and mood; however, they experienced a rebound of symptoms once gabapentin was discontinued (11).

Pregabalin
Pregabalin is a structural analog to GABA that may have a novel mechanism of action by binding to a subunit of voltage-dependent calcium channels (12).

Social Phobia
Feltner and colleagues conducted an 11-week randomized, double-blind study of 135 patients with SP, using high-dosage pregabalin (600 mg daily), low-dosage pregabalin (150 mg daily) or placebo (13). Only the high-dosage group showed significantly improved SP symptoms, compared with placebo.

GAD
In a randomized, double-blind study of 276 patients, Pande and colleagues compared high-dosage (600 mg daily) and low-dosage (150 mg daily) pregabalin with lorazepam (6 mg daily) and placebo in treating GAD (14). Both high-dosage pregabalin and lorazepam demonstrated significantly greater anxiolytic effects than did placebo.

Lydiard and colleagues conducted a second double-blind, placebo-controlled study of GAD, comparing the efficacy of pregabalin with that of alprazolam, venlafaxine and a placebo (15). Pregabalin, at either 300 mg daily or 600 mg daily, was significantly better than placebo at improving psychic and somatic anxiety symptoms. Compared with venlafaxine and alprazolam, pregabalin was associated with better early (one-week) improvement.

Montgomery and colleagues compared pregabalin with venlafaxine and alprazolam in terms of the speed of onset in treating GAD symptoms (16). They found that pregabalin demonstrated more rapid treatment response than venlafaxine and that it was equivalent to alprazolam.

In a study combining data from five double-blind, placebo-controlled trials of pregabalin treatment for GAD, Pollack and colleagues evaluated the Hamilton Anxiety Rating Scale (HARS) scores of patients with low and high baseline depression (17). Pregabalin treatment resulted in significant improvement, compared with placebo, for all dosages (200 mg daily, 300 mg daily, 400 to 450 mg daily or 600 mg daily) in both high and low baseline depression. Pregabalin at all dosages was also associated with significant improvements in depressive symptoms, compared with placebo. Further, pregabalin demonstrated equivalent efficacy in improving depressive symptoms in a venlafaxine comparator trial (17).

Valproic Acid (VPA) or Divalproex
Divalproex is primarily taken as sole or adjunctive therapy for the treatment of simple or complex absence seizures or generalized seizures with tonic-clonic manifestations; it is taken adjunctively by patients with multiple seizure types. VPA has also been indicated for treatment of mania in BD. Although its exact mechanism
of action is unknown, it has been suggested that VPA increases the brain concentrations of GABA.

**Panic Disorder**

Case reports have documented success in treating PD comorbid with alcoholism (18), substance abuse (19), benzodiazepine withdrawal (20) and multiple sclerosis (21), as well as success in cases of treatment-resistant PD (22,23). In a case series of four patients with treatment-resistant PD, improvement was reported with a combination of VPA and clonazepam (23). Primeau and colleagues conducted a seven-week open trial of 10 patients with PD or agoraphobia with panic attacks. The patients were treated with VPA 500 mg daily to a maximum of 2,250 mg daily (24). The authors noted statistically significant improvements in PD symptoms. Similar results were found in a six-week open trial of 12 patients with PD treated with VPA. The improvement was sustained at 18-month followup (25).

Lum and others conducted a six-week randomized, double-blind, placebo-controlled study of 12 panic disorder patients treated with VPA (26). They noted significant improvements in the VPA patient group, compared with the placebo group.

**PTSD**

Symanski and Olympia recorded two case reports demonstrating improvements in PTSD symptoms with VPA treatment (specifically, prominent reductions in irritability) (27). Two open-label studies also demonstrate success with VPA treatment (28,29).

**OCD**

The use of VPA to treat OCD has been documented in a case report and in an open-label trial in patients who had discontinued conventional antiobsessional medication owing to side-effects (30,31). Deltito described successful outcomes in eight of 10 patients using VPA (250 mg daily to 2,500 mg daily) (31). Typical antiobsessional pharmacotherapy was restarted and showed improved tolerability. A case report by Cora-Locatelli and others also describes the efficacious use of VPA as pretreatment in a patient who could not tolerate the side-effects of fluoxetine (30). In both reports, SSRIs were added and increased tolerability.

**Social Phobia**

VPA has shown mixed results in the treatment of SP, as described in 2 reports. In an open trial of VPA, Nardi and colleagues treated 16 subjects suffering from generalized SP with dosages of 500 to 1,500 mg daily for 1 to 9 months (32). They considered all the patients to be nonresponders to VPA. In a 12-week open trial of VPA, Kinrys and others treated 17 subjects suffering from SP with dosages of 500 to 2,500 mg daily. The intent-to-treat analysis considered 41.1 per cent to be responders according to the CGI-I, with a mean LSAS drop of 21.3 points (33).

**Tiagabine**

Tiagabine inhibits the reuptake of GABA by inhibiting the GAT-1 transportation system but does not act directly on GABAergic receptors (34).

**PTSD**

In a six-week open-label case series examining the use of adjunctive tiagabine in PTSD, six patients with comorbid mood disorders were treated with tiagabine two to four mg daily. Significantly reduced anxiety was reported after one week and maintained at six weeks (35). Berigan reported the use of adjunctive tiagabine in a patient with comorbid PTSD and major depressive disorder (36). This report accredited reduced reexperiencing symptoms to the addition of tiagabine. Significantly reduced PTSD symptoms with tiagabine have also been reported in an open-label trial of seven PTSD patients (37).

**Panic Disorder**

In an open trial of tiagabine, five patients with PD and PD with comorbidity showed significantly reduced anxiety symptoms (38). The tiagabine dosage was approximately 10 mg daily. Similar success was found in a case series of four patients treated with tiagabine, which reported reduced anxiety, agoraphobia and panic attacks (39). Zwanzger and colleagues recently reported that tiagabine was also shown to reduce cholecystokinin-tetrapeptide (CCK-4)–induced panic attacks in healthy subjects (40).

**GAD**

Gruener reported significantly reduced anxiety in five patients with GAD and comorbid major depression or neuropathic pain, or both, who were treated with adjunctive tiagabine six mg daily (38). Improvement was noted at two weeks, and the effect was maintained for the eight-week trial. Papp and Ray reported similar findings with a mean dosage of tiagabine nine mg daily in the eight-week trial of 25 patients with GAD (41). Rosenthal and Dolnak conducted a 10-week open-label, positive-controlled, blind rater study of 40 patients randomized to tiagabine or paroxetine (42). Tiagabine and paroxetine were equally effective in significantly reducing anxiety and depression, along with improving sleep and overall functioning.

**Other**

Successful use of tiagabine as augmentation therapy has also been reported in an open-label study of 20 patients with various anxiety disorders (specifically, GAD, PTSD, PD and SP) being primarily treated with SSRIs (78 per cent). Tiagabine significantly improved anxiety from baseline, with 59 per cent of patients achieving remission (43). Tiagabine has also been found to successfully aid symptoms of anxiety, as well as rage and aggression, in a patient group with various DSM-IV diagnoses, including anxiety disorders and depression (44).
Carbamazepine

Carbamazepine is indicated for epilepsy and is useful in treating partial and complex seizures. It is also indicated for treatment of acute mania and for prophylaxis in BD. Its primary mechanism of action is through blockade of voltage-gated sodium channels in neuronal cell membranes, which prevents the release of excitatory neurotransmitters from nerve terminals.

Panic Disorder

In an open-label trial, 34 patients with PD and PD with agoraphobia were treated with carbamazepine at a mean dosage of 419 mg daily for two to 12 months; 58 per cent showed a good response to the medication (45). However, in a controlled study of 14 patients by Uhde and colleagues, carbamazepine was not found effective in treating PD at a mean dosage of 679 mg daily and a mean treatment duration of 66 days (46).

PTSD

Several open-label studies have suggested that carbamazepine may be a useful treatment for PTSD. Lipper and colleagues reported that seven of 10 patients with PTSD were rated as moderately or very much improved on the CGI-I (47). Patients also demonstrated reduced frequency of reexperiencing symptoms. In a case series of 10 patients with PTSD, Wolf and colleagues reported clinical improvements, particularly in violent behaviour (48).

Carbamazepine use, at dosages of 300 mg daily to 1,200 mg daily, has also been reported in a group of 28 children aged eight to 17 years suffering from PTSD and PTSD with comorbidity (49). Of the 28 patients, 22 became free of PTSD symptoms, while six patients reported infrequent nightmares (49).

OCD

We found a single case report describing a woman, aged 27 years and suffering with OCD, who improved when treated with a combination of carbamazepine (500 mg daily) and clomipramine (200 mg daily). Significant improvements in anxiety, distress and habitual checking were reported (50).

Phenytoin

Phenytoin is used to control generalized tonic-clonic and psychomotor seizures. It appears to inhibit seizure activity through its action on the motor cortex. Its anticonvulsive effects likely come from its promotion of sodium efflux, which stabilizes firing thresholds against hyperexcitability.

Panic Disorder

McNamara and Fogel documented three case reports of patients who experienced a complete cessation of panic attacks as a result of treatment with phenytoin (51). These patients also had abnormal temporal lobe EEG patterns, comparable to interictal temporal lobe epilepsy. It was unclear whether the cessation in panic attacks was owing to the anticonvulsant or the psychotropic properties of the medication.

References

35. Lara ME. Tiagabine for augmentation of antidepressant treatment of post-traumatic stress disorder. Presented at the 22nd National Conference of the Anxiety Disorders Association of America; 2002; Austin (TX).
37. Davidson JRT. Novel GABAergic treatments in neuropsychiatric disorders. Presented at the Anxiety Disorders Association of America’s 23rd National Conference; 2003; Toronto (ON).
38. Gruener D. Tiagabine as an augmenting agent for the treatment of anxiety. Presented at the 22nd National Conference of the Anxiety Disorders Association of America; 2002; Austin (TX).
44. Hoffman DA. Tiagabine for the treatment of symptoms of rage, aggression, and anxiety. Presented at the 156th Annual Meeting of the American Psychiatric Association; 2003; San Francisco (CA).