REVIEW ARTICLE

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Antiepileptic Drugs in the Treatment of Anxiety Disorders

Role in Therapy

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Abstract

Pharmacotherapy for anxiety disorders is an active area of research. A variety of drug groups have been shown to be effective in treating many of the anxiety disorders, with selective serotonin reuptake inhibitors (SSRIs) being considered first-line agents for virtually all anxiety disorders. There is a clinical need for alternative drug treatments, as many patients do not achieve a complete response and experience significant adverse effects. The successful use of antiepileptic drugs in mood disorders has led clinicians and researchers to investigate their potential efficacy in other psychiatric disorders, particularly in anxiety disorders.

There have been a number of investigations conducted in the form of case reports, case series and open-label trials, suggesting the potential usefulness of antiepileptic drug treatment in a variety of anxiety disorders. More reliable evidence for the use of antiepileptic drugs in anxiety disorders can be gleaned from recent placebo-controlled trials. Thus far, the strongest placebo-controlled evidence has demonstrated the efficacy of pregabalin in treating social phobia and generalised anxiety disorder, while smaller or less robust controlled trials have suggested the potential efficacy of gabapentin in social phobia, lamotrigine in post-traumatic stress disorder, and valproic acid in panic disorder.

Antiepileptic drugs may have a place in the treatment of anxiety disorders; however, further investigation is warranted to determine in what circumstances they should be used as monotherapy or as augmenting agents in individuals who are partially or non-responsive to conventional therapy.

1. Pharmacological Treatment of Anxiety Disorders

Pharmacological treatments for anxiety disorders have been rapidly evolving in recent years and a variety of drug groups have been shown to be effective. Benzodiazepines have long been used to treat anxiety; however, the development of tolerance to these drugs has made them less favourable treatments.[1,2] Selective serotonin reuptake inhibitors (SSRIs) have emerged as the current gold standard. Despite such widespread use, SSRIs are only effective in approximately 50–60% of patients, and can be associated with significant adverse effects. There are also concerns regarding the long-term efficacy of SSRIs, with reported relapses or 'poop-out' having been known to occur after extended use.[3] There is a clinical need for alternative medication treatments for anxiety disorders, in the form of either monotherapy or as augmentation agents.

Antiepileptic drugs have been widely used in the treatment of mood disorders and have become first-line treatments for bipolar disorder.[4,5] The successful use of antiepileptic drugs in mood disorders has led clinicians and researchers to investigate their potential efficacy in other psychiatric disorders, particularly in anxiety disorders.

This article attempts to review the small but emerging literature on the use of antiepileptic drugs in anxiety disorders. Information for this review was obtained from a Medline search and a review of abstracts from major psychiatric congresses (Annual Meeting of the American Psychiatric Association, National Conference of the Anxiety Disorders Association of America, Annual Meeting of the American College of Neuropsychopharmacology). Each anxiety disorder is reviewed focusing on available data that has been presented or published for each antiepileptic drug that has been studied in that disorder.

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1.1 Rationale for Antiepileptics in Anxiety Disorders

The notion of using antiepileptic drugs in anxiety disorders can find a basis in emerging constructs describing fear circuits in the brain. Numerous brain regions are likely to be involved in the expression of fear, but the amygdala is thought to play a key role because of its ability to link sensory stimuli with affective outcomes and initiate emotionally appropriate behaviours.[6] Various pathologies, such as anxiety disorders and addiction, could be a manifestation of an 'over-expression' of these amygdala-based, conditioned emotional associations.[7] This 'over-expression' may result from a failure of proper inhibitory control in the amygdala.

GABA is the primary inhibitory neurotransmitter in the CNS. The inhibitory action of GABA counterbalances the excitatory activity of the neurotransmitter glutamate. The homeostasis between GABA and glutamate controls CNS arousal and neuronal excitability. Maintaining this balance prevents over-excitability, which is known to occur in seizure disorders but is also thought to play a role in pathologic anxiety,[8] potentially through the 'over-expression' of conditioned fear associations, as previously mentioned.

Abnormalities in both GABA systems and glutamatergic systems have been associated with various anxiety disorders. For example, occipital GABA levels decreased by as much as 22% in panic disorder patients compared with healthy controls.[9] A dysfunction in $GABA_A$ receptor binding is also thought to play a role in anxiety disorders, stemming from the observation of diminished response to exogenous benzodiazepines in individuals with anxiety.[10] A potential glutamatergic dysfunction has recently been associated with obsessive-compulsive disorder (OCD), based on a neuroimaging study describing an increase in caudate glutamatergic levels of treatment-naive paediatric OCD patients.[11] It has also been hypothesised that a glutamatergic abnormality in social anxiety may be a key component in the dysfunctional neurocircuitry. Increased levels of glucocorticoids in response to stress are thought to stimulate the release of hippocampal glutamate, which may inhibit neurogenesis. A decrease in neurogenesis may be associated with social phobia, as found in animal models of social dominance with subordinate status being linked with a marked decrease in new cells in the dentate gyrus.[12]

Various antiepileptic drugs are thought to modulate GABA and glutamate, therefore, treating anxious patients with such agents may restore the homeostasis between these two neurotransmitters and decrease neuronal over-excitability, particularly in the amygdala.

2. Social Phobia

Social phobia (social anxiety disorder) is characterised by a marked and persistent fear of social or performance situations due to an excessive fear of embarrassment or humiliation.[13] Individuals with social phobia typically fear and avoid public speaking, participating in small groups, dating, speaking to authority figures, attending parties and speaking with and meeting strangers.

Numerous drug classes have been found to be efficacious in social phobia, including SSRIs,[14-16] serotonin and norepinephrine reuptake inhibitors (SNRIs),[17] monoamine oxidase inhibitors (MAOIs)[18-20] and reversible inhibitors of monoamine oxidase-A.[21,22] Paroxetine, sertraline and venlafaxine have received regulatory approval for the treatment of social phobia in several countries, including the US.

2.1 Topiramate

Topiramate has been used both adjunctively and as monotherapy in epileptic patients. Topiramate appears to have several mechanisms of action. It has been shown to enhance the activity of GABA at non-benzodiazepine sites, to inhibit glutamate via α-adenosine monophosphate/kainate subreceptors and appears to block voltage-gated sodium channels. It is also a weak inhibitor of carbonic anhydrase isoenzymes CAII and CAIV.[23]

Van Ameringen et al.[24] evaluated the effectiveness of topiramate in treating social phobia in a 16-week open-label trial of 23 patients with generalised social phobia. The mean dose of topiramate at endpoint was 222.8 ± 141.8 mg/day, with a dose range of 25–400 mg/day. In the intention-to-treat (ITT) sample 45.1% (12/23) of patients were re-

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sponders (Clinical Global Impression of Improvement [CGI-I] scale score of ≤2) and a significant improvement was found from the baseline measure to endpoint on the Liebowitz Social Anxiety Scale (LSAS). Significant changes in self-report measures of social anxiety were demonstrated; however, no changes were found on measures of depression or generalised anxiety. Six of the 23 participants (26.1%) achieved remission status, defined as an endpoint LSAS score ≤30. The most common adverse events included weight loss, paraesthesia and headache, with only five patients withdrawing from the study as a result of them. Although this was an open-label design, these results suggest that topiramate may have a specific effect on symptoms of social phobia. This finding is particularly intriguing given the purported mechanism of action of topiramate involving both glutamate and GABA neurotransmitter systems. The remission rate in this study was similar to that found in a recent placebo-controlled trial examining the treatment of social phobia with venlafaxine.[25] However, a major drawback with this treatment may be individuals' ability to tolerate the bothersome adverse effects, particularly cognitive impairment.

2.2 Gabapentin

Gabapentin is an antiepileptic drug that increases the release of nonsynaptic GABA from the glial cells, thereby decreasing neuronal over-excitability.[8]

The effectiveness of gabapentin in treating social phobia was examined in a placebo-controlled study by Pande et al.[26] Sixty-nine patients were randomly assigned to a 14-week double-blind treatment of either gabapentin, with a varying dose of 900–3600 mg/day, or a placebo. The treatment group demonstrated significantly more symptom reduction than the control group, as measured by the LSAS ($p = 0.008$), the Brief Social Phobia Scale (BSPS) [$p = 0.007$], and the Social Phobia Inventory (SPIN) [$p = 0.008$]. In ITT analysis twice as many patients taking gabapentin were considered responders (32% for gabapentin vs 14% for placebo), defined by a decrease of at least 50% on the LSAS; however, this difference in response rate did not reach significance ($p = 0.08$). The Clinical Global Impression of Change (CGI-C) scale response (defined as 'much' or 'very much improved') rate was 38.2% for the gabapentin group compared with 17.1% for the placebo group. Adverse events that occurred significantly more in the gabapentin group included dizziness, somnolence, nausea, flatulence and decreased libido. Of the 44% of individuals, who withdrew from this study before completion, 21% of those taking gabapentin withdrew because of adverse events compared with 11% of the placebo group. Although gabapentin did not differ from placebo on the primary outcome measure (≥50% decrease in LSAS) there was a suggestion from secondary outcome measures that there may be a treatment effect of gabapentin on social phobic symptoms, albeit moderate.

2.3 Pregabalin

Pregabalin is a structural analogue to GABA which may have a novel mechanism of action by binding to a subunit of voltage-dependent calcium channels.[27]

The effectiveness of pregabalin in treating social phobia was demonstrated by a double-blind, placebo-controlled study conducted by Feltner et al.[28] In this study 135 patients with social phobia were randomly assigned to 11 weeks of high-dose pregabalin (600 mg/day; $n = 47$), low-dose pregabalin (150 mg/day; $n = 42$) or a placebo ($n = 46$). In ITT analysis significant improvements were observed in the high-dose group compared with placebo, as measured by the LSAS total score, as well as the LSAS fear and avoidance subscales and the BSPS fear subscale. Furthermore, the rate of response (defined as a CGI-I rating of 'much' or 'very much' improved) was 43% (20 of 47) for the high-dose group compared with 22% (10 of 46) for the placebo group. The low-dose group showed greater improvements over the placebo group; however, the difference did not reach statistical significance. Pregabalin was also found to be relatively well tolerated, with mild-to-moderate somnolence and dizziness being the most common adverse effects associated with high-dose pregabalin. Of the 30.4% of patients who withdrew from the study, 23.4% of those in the high-dose pregabalin group withdrew as a result of adverse events, compared with 9.5% in the low-dose group and 8.7% in the placebo group.

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This study suggests that pregabalin may be a promising new agent in the treatment of social phobia.

2.4 Valproic Acid

Valproic acid is primarily taken for monotherapy or adjunctive therapy for the treatment of simple or complex absence seizures, generalised seizures with tonic-clonic manifestations, and adjunctively for patients with multiple seizure types. Valproic acid has also been indicated for treatment of mania in bipolar disorder. Although its exact mechanism of action is unknown, it has been suggested that valproic acid increases the brain levels of GABA.

Valproic acid has shown mixed results in the treatment of social phobia, as described in two reports. Nardi et al.[29] treated 16 patients with generalised social phobia in an open-label trial of valproic acid with doses of 500–1500 mg/day (mean dose 1071 ± 75 mg/day) for 1–9 months. All patients were considered nonresponders to valproic acid.[29] In another study, Kinrys et al.[30] treated 17 patients with social phobia in a 12-week open-label trial of valproic acid with doses of 500–2500 mg/day (mean dose 1985 ± 454 mg/day). In the ITT analysis 41.1% of patients were considered responders by CGI-I, with a mean decrease in LSAS of 19.1 points. Adverse events included nausea, somnolence, dizziness and fatigue. Only one of 17 participants withdrew because of adverse events.[30] Conclusions that can be deemed from this study are limited as a result of the small sample size and open-label design. The contradicting results of these two studies would suggest the need for further investigations of valproic acid in social phobia.

2.5 Tiagabine

Tiagabine is the only selective GABA uptake inhibitor. It increases the synaptic GABA availability by selective inhibition of the GABA transporter 1, the most abundant GABA transporter.[31,32] It has been indicated for add-on treatment of partial seizures. GABA has been thought to play an important role in the pathophysiology of certain anxiety disorders, including social phobia, making tiagabine an interesting agent for investigation.

Tiagabine monotherapy (mean dose 10 mg/day) for social phobia was investigated by Papp and Ninan[33] in a 12-week open-label trial of 57 patients with social phobia, 25 of whom completed the study. Of the 32 patients that withdrew from the study, nine discontinued as a result of adverse events and three because of lack of efficacy. In ITT analysis significant reductions in social phobia symptoms was found as measured by the LSAS and SPIN. Significant improvements in quality of life were also found. In the ITT analysis of 51 patients, 35% of patients were considered responders by ≥50% reduction in LSAS, while 41% of patients (21 of 51) responded based on CGI-I score of ≤2, and 24% of patients were considered in remission (LSAS ≤30). Most common adverse events included somnolence (32%) and dizziness (25%).[33]

Kinrys et al.[34] conducted a retrospective analysis of a cohort of patients (n = 14) treated with tiagabine adjunctively who have not responded to an SSRI. Tiagabine was taken adjunctively for a mean duration of 30.6 weeks at a mean dose of 16.4 ± 6.9 mg/day (ranging from 8 to 83 mg/day), with an SSRI and, in some cases, other medications including quetiapine, clonazepam and bupropion. In this cohort, 64.2% of patients (9 of 14) met response criteria (CGI ≤2) at endpoint, and 35.7% of patients (5 of 14) met remission criteria (LSAS ≤30). Symptom response and remission was maintained in those patients at 28 weeks.[34]

These two open-label reports suggest that tiagabine may be useful as a monotherapy or an augmentation therapy for treatment-resistant social phobia. However, the small sample size, open-label design and, in the augmentation study, the use of a variety of concomitant medication may limit the generalisability of these results.

2.6 Levetiracetam

Recently, a trial of 20 patients with generalised social phobia was conducted using the novel antiepileptic drug, levetiracetam. This agent reduces currents through high voltage-activated calcium channels, and acts via a unique binding site, the synaptic vesicle protein SV2A.[35] Simon et al.[36] gave levetiracetam to patients with generalised social phobia for 8 weeks, with doses initiated at 250 mg/day and flexibly titrated to 3000 mg/day (mean dose 2013 mg/day). Thirteen of the 20 patients completed the trial, and of those patients three

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discontinued because of adverse events (drowsiness and nervousness). In ITT analysis there was a significant decrease in LSAS from baseline to endpoint (20.5 point decrease). A significant decrease in symptoms as measured by the Hamilton Rating Scale for Anxiety (HAM-A) and the Clinical Global Impression of Severity (CGI-S) scales was also found.[36] This study suggests that levetiracetam may be useful in the treatment of generalised social phobia; however, further evaluation would be warranted with a larger sample size and a controlled design.

3. Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a pathological response resulting from exposure to a traumatic stressor. Three clusters of symptoms occur in PTSD: (i) persistent re-experiencing of the traumatic event (i.e. dreams, distressing recollections); (ii) avoidance of stimuli associated with the trauma as well as numbing or detachment; and (iii) persistent symptoms of increased arousal.[13]

Evidence from placebo-controlled trials have demonstrated the efficacy of SSRIs in treating PTSD, making these antidepressants first-line treatment agents for PTSD.[37] Fluoxetine,[38,39] sertraline[40] and paroxetine[41,42] have all demonstrated efficacy in placebo-controlled trials. Other medications have also demonstrated efficacy in PTSD, including the MAOI phenelzine[43] as well as the tricyclic antidepressants (TCAs) amitriptyline[44] and imipramine.[43] Recent evidence suggests that antiepileptic drugs may be a tolerable and efficacious alternative treatment for PTSD.

3.1 Lamotrigine

Lamotrigine is used as either an adjunct or monotherapy agent for epilepsy. It is thought to produce anti-seizure effects by its action on voltage-sensitive sodium channels, and subsequent inhibition of the release of glutamate and aspartate. It has been studied in mood disorders and has been found to be effective for the treatment of bipolar depression.[45]

A placebo-controlled trial was conducted by Hertzberg et al.[46] to evaluate the effectiveness of lamotrigine in treating PTSD. Ten patients received lamotrigine and four patients received placebo for up to 10 weeks (mean dose at endpoint 380 mg/day). Improvements in avoidance or numbing and re-experiencing (i.e. flashbacks, nightmares) symptoms, as measured by the Duke Global Rating for PTSD, were found with lamotrigine while no improvements were measured in the control group. Fifty percent (five of ten) of patients treated with lamotrigine were classified as treatment responders (compared with 25% [one of four] in the placebo group). Two of the ten lamotrigine patients developed a rash leading to discontinuation, while two of four placebo patients also discontinued the study because of a rash. Other adverse effects were felt to be mild and included sweating, drowsiness, poor concentration, thirst, restlessness and sexual dysfunction.[46] Although this study uses a placebo-controlled design, the results must be interpreted with caution. The small sample size did not allow for statistical analysis of the quantifiable measures and only one placebo patient completed the study. Further studies with larger samples are needed to further assess the potential benefits of lamotrigine in PTSD.

3.2 Topiramate

One open-label trial of topiramate in PTSD has been reported. In a study by Berlant and Kammen,[47] 35 PTSD patients were given topiramate as monotherapy or of as adjunctive therapy, for a mean duration of 33 weeks. It was found that topiramate reduced nightmares in 79% of patients and reduced intrusions or flashbacks in 86% of patients, based on self-report at endpoint. Fourteen of the 17 patients who had completed the PTSD Checklist-Civilian Version after 4 weeks of treatment had a score of ≤50 (this is below the standard cut-off score for active PTSD). Symptom improvements were reported with both topiramate monotherapy and adjunctive therapy, with a monotherapy mean dose for full response of 43 mg/day (range 25–75 mg/day) compared with 97 mg/day (range 25–500 mg/day) for a full response with adjunctive therapy. Nine patients discontinued treatment because of adverse effects, which included urticaria, eating cessation, acute narrow-angle glaucoma, severe headache, overstimulation/panic, memory concerns and one occurrence of emergent suicidal ideation. The topiramate doses

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used in this study were quite low compared with those that have been used in other psychiatric illnesses.[48]

Various methodological limitations make the results of this study difficult to interpret. Only half the sample completed a standardised self-report measure of PTSD and the measure that was reported was only included in the results after 4 weeks of treatment, which was not likely to be an adequate duration of treatment for accurately measuring response. The study included a heterogeneous population including different subtypes of PTSD (hallucinatory PTSD vs nonhalucinatory PTSD), significant comorbidity (comorbid bipolar disorder), as well as both adjunctive and monotherapy. Further placebo-controlled trials using topiramate either specifically as monotherapy or adjunctive therapy with a more homogeneous sample would allow for a better evaluation of its usefulness in PTSD.

3.3 Gabapentin

Case reports have described the successful treatment of PTSD with gabapentin.[49,50] A reduction in nightmares and anxiety was reported in patients experiencing PTSD and comorbid depression, treated with gabapentin 1200 mg/day.[49] Hamner et al.[50] conducted a retrospective chart review of 30 patients diagnosed with PTSD who were treated with adjunctive gabapentin. Sixty-seven percent of patients had comorbid major depressive disorder. In nearly every case, gabapentin was added to target sleep disturbance symptoms associated with PTSD. It was found that 77% of patients demonstrated 'moderate' or 'marked' improvements in sleep duration, as well as a decrease in the frequency of nightmares. The most common adverse events were sedation and mild dizziness.[50] The results of this study should be interpreted with caution given its retrospective nature, as well as the inclusion of patients with concomitant multiple sedating medications. Further controlled research is needed to evaluate the efficacy of gabapentin in treating the core symptoms of PTSD, as well as its use as an adjunctive agent to treat nightmares and insomnia.

3.4 Valproic Acid

Szymanski and Olympia[51] recorded two patients demonstrating improvements in PTSD with valproic acid treatment of 1000 and 1500 mg/day, respectively, showing prominent reductions in irritability. In an open-label trial Fesler[52] treated 16 Vietnam War veterans with valproic acid (mean dose 109.3 mg/day) for 1 year. The majority of patients experienced significant improvements in hyperarousal symptoms and avoidant symptoms; however, little improvement was found in the re-experiencing or intrusive symptoms of PTSD. The most common adverse events were gastrointestinal, which included abdominal cramps, indigestion, nausea and constipation. In another open-label trial of 21 patients with combat-induced PTSD treated with valproic acid (mean dose 1840 mg/day) similar results were found.[53] Unlike in the previous study,[52] however, symptom reduction was measured in all three symptom clusters using the Clinician-Administered PTSD scale. Six patients discontinued valproic acid because of intolerable adverse effects, including rash, diarrhoea and nausea.[53]

Another, more recent, open-label trial[54] suggests, however, that valproic acid may not be efficacious in non-combat-related PTSD. In a trial of ten patients with PTSD related to accidents, witnessing the death of a loved one and sexual/physical abuse, valproic acid monotherapy was initiated at 250 mg/day and increased up to 2000 mg/day (mean dose 1400 ± 380 mg/day). No improvements were found in PTSD or depressive symptoms using the Posttraumatic Diagnostic Scale, the Impact of Event Scale-Revised and the Beck Depression Inventory, after 4 and 8 weeks of treatment.

Open-label trial data thus far suggests that valproic acid may be useful in PTSD; however, there are conflicting reports regarding its efficacy in treating all the core symptom clusters of PTSD.

3.5 Tiagabine

An open-label case series conducted by Lara[55] examined the use of tiagabine to augment antidepressant therapy in PTSD. Six patients were included in the case series: two with comorbid bipolar depression and four with comorbid major depression. Patients started tiagabine at 2–4 mg/day, in-

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creasing to a maximum of 16 mg/day. Significant reduction in anxiety was found after 1 week of therapy, and the effect was maintained at 6 weeks, as measured by the change in the baseline score of the Davidson Trauma Scale.[55] Aggression levels were also significantly reduced. Similar success in treating one patient with PTSD and comorbid major depression with adjunctive tiagabine was reported by Berigan.[56] In this case report, a reduction of re-experiencing symptoms was accredited to the addition of tiagabine. In addition, an open-label trial of seven patients also found positive results with the use of tiagabine (mean dose 7.3 mg/day) in treating PTSD.[40]

A recent study by Davidson et al.[57] also examined the efficacy of tiagabine in PTSD. This study involved a 12-week open-label phase followed by a double-blind randomisation of patients who completed the open-label phase to tiagabine continuation or a tapering of tiagabine then switching to placebo, for an additional 12 weeks. In the ITT sample of the open phase (n = 26) of tiagabine (mean dose 12.8 ± 4.3 mg/day) significant improvements were observed in all measures of PTSD, depression, general anxiety, social anxiety, resilience and disability. After the double-blind, placebo-controlled discontinuation phase (n = 18) there was no significant difference between the two groups, with gains being maintained on all outcomes.[57] The potential benefits of tiagabine in PTSD need to be further evaluated in a controlled study of acute PTSD.

3.6 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 prophylaxis in bipolar disorder. Its primary mechanism of action is through blockade of voltage-gated sodium channels in neuronal cell membranes, thus preventing the release of excitatory neurotransmitters from nerve terminals.

Several open-label studies have suggested that carbamazepine may be a useful treatment for PTSD. Lipper et al.[58] reported that seven of ten patients who met the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, criteria for PTSD and a comorbid personality disorder were rated as 'moderately' or 'very much' improved on the CGI-I scale after treatment with carbamazepine (mean dose 780 mg/day). Patients also demonstrated a reduction in the frequency and intensity of flashbacks, nightmares and intrusive thoughts, as measured by interview-rated scales and self-report scales.[58] Wolf et al.[59] also reported the treatment of ten PTSD patients with carbamazepine, and found improvements in the clinical condition of the patients, as measured by staff observations and self-report, with particular improvements in violent behaviour. No standardised measures were used to assess symptom improvement. The use of carbamazepine (300–1200 mg/day), in a group of 28 sexually abused children aged 8–17 years with PTSD and PTSD with comorbidity (attention deficit hyperactivity disorder, depression, oppositional defiant disorder, polysubstance abuse), has also been reported. Of the 28 patients, 22 became free of PTSD symptoms while six reported infrequent abuse-related nightmares.[60] No standardised measures were used and, given the open-label design, clinician bias and placebo effect must be taken into consideration.

3.7 Vigabatrin

Vigabatrin, a specific GABA transaminase inhibitor, is used as an antiepileptic drug and also to treat hyperekplexia (startle disease) in neonates. A series of five PTSD cases whose treatment was augmented with vigabatrin has been reported.[61] Vigabatrin was added to treat hypervigilance and startle in these patients who had not improved with other treatments. All five patients tolerated the treatment well and had a rapid amelioration of their exaggerated startle response. There were no changes found in other PTSD symptoms.[61]

3.8 Oxcarbazepine

Oxcarbazepine is structurally related to carbamazepine; however, it is not metabolised by 10,11-epoxide, which is thought to be responsible for a decrease in the adverse effects typically seen with carbamazepine. Its primary mechanism of action is thought to involve the blockage of voltage-dependent sodium channels. One case report described improvements in PTSD symptoms with oxcarbazepine augmentation.[62] This report describes

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the case of a 46-year-old man with chronic PTSD who has been unresponsive or intolerant to numerous pharmacological treatments, including the antiepileptic drugs carbamazepine and valproic acid. Then his treatment was augmented with 300 mg/day of oxcarbazepine, titrated up to 900 mg/day along with 150 mg/day of sertraline and 0.5 mg/day of clonazepam. The patient reported experiencing less frequent and severe nightmares, as well as improvements in all areas of functioning. Gains were maintained at 4-month follow-up.[62]

4. Panic Disorder

Panic disorder is characterised by recurrent, unexpected panic attacks, defined as discrete periods of intense anxiety and feelings of fearfulness, terror and often impending doom. There is persistent concern regarding the panic attacks and it may occur with or without agoraphobic avoidance. Situations typically avoided by patients with panic disorder include being outside the home alone, being in a crowd, being on a bridge, or travelling on a bus, train or automobile.[13]

TCAs and MAOIs were among the first pharmacological agents shown to be efficacious in the treatment of panic disorder.[63-65] Currently, benzodiazepines[66,67] and SSRIs,[68-72] either alone or in combination, are used as standard treatment for panic disorder.

4.1 Gabapentin

Successful treatment of panic disorder with gabapentin has been documented in case reports.[73] Pande et al.,[74] in a double-blind, placebo-controlled study, randomly assigned 103 patients with panic disorder to gabapentin 600–3600 mg/day or a placebo for 8 weeks. The effect of treatment on panic disorder symptoms was measured with the Panic and Agoraphobia Scale (PAS). Although the difference in symptom severity, as measured by the PAS, was insignificant between the treatment and placebo groups for the entire patient sample, a significant improvement was found in a severely ill subsample (those with a PAS baseline ≥20; $p = 0.04$).[74] However, no significant difference in responders was found between placebo and gabapentin in those with a PAS baseline ≥20 (26.9% placebo vs 37% gabapentin; $p = 0.437$), or between those with a PAS baseline <20 (66.7% placebo vs 45% gabapentin; $p = 0.223$). A total of 12% of patients in the gabapentin group discontinued the study because of adverse events compared with 4% in the placebo group.[74] Common adverse events included somnolence, headache and dizziness. Given this negative result, gabapentin should potentially be reserved for use as an adjunctive therapy or for treatment of non-responders to standard therapies.

4.2 Valproic Acid

The antipanic effects of valproic acid have been described in several case reports documenting successful treatment of panic disorder with comorbid alcoholism,[75] substance abuse,[76] benzodiazepine withdrawal[77] and multiple sclerosis.[78] A case series by Ontiveros and Fontaine[79] described the improvements of four patients with treatment-resistant panic disorder using a combination of valproic acid and clonazepam.

Further support of the effectiveness of valproic acid in treating panic disorder has come from open-label studies. Primeau et al.[80] conducted an open-label trial, including ten patients with panic disorder or agoraphobia with panic attacks. Patients were treated with valproic acid for 7 weeks with an initial dose of 500 mg/day, and increased to a maximum of 2250 mg/day. Significant improvements were noted for both panic and anxiety symptoms. Similar results were found in a 6-week open-label trial of 12 patients with panic disorder treated with valproic acid conducted by Woodman and Noyles.[81] All 12 patients demonstrated moderate or marked improvement after the 6-week trial. The improvements gained from the valproic acid treatment were sustained at 6-month and 18-month follow-up. Other open-label trials have demonstrated the ability of valproic acid to block lactate-induced panic attacks,[82] as well as to treat patients with panic disorder and mood instability who are resistant to conventional therapy.[83]

Lum et al.[84] conducted a double-blind, placebo-controlled study with a 2×2 crossover design, of valproic acid treatment for panic disorder in 12 patients, with doses achieving a valproic acid plasma level between 60 and 120 mg/mL. Significant improvements in the valproic acid patient group

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compared with the placebo group were noted based on the CGI-S and CGI-I scales, with marked reduction in the length and intensity of panic attacks, as well as psychic and somatic symptoms of anxiety, as measured by HAM-A scores. Five patients reported adverse events while taking valproic acid, which included gastrointestinal dysfunction, dizziness and somnolence.[84] These preliminary results suggest that valproic acid may be an effective treatment for panic disorder which demonstrates a long-term treatment effect; however, larger placebo-controlled trials with long-term follow-up are needed to confirm these findings.

4.3 Tiagabine

In an open-label trial of five patients Gruener[85] reported the improvements from tiagabine 20 mg/day in panic disorder, as well as panic disorder with comorbidity. Anxiety was found to be significantly reduced in all patients at 2 weeks, and this reduction was maintained for the entire treatment period (8 weeks). Similar success was found in a case series of four patients treated with tiagabine, where reductions in anxiety, agoraphobia and panic attacks were found.[86]

Tiagabine has also been shown to reduce panic in cholecystokinin-tetrapeptide (CCK-4) induced panic in healthy individuals. Zwanger et al.[87] gave 15 mg/day of tiagabine to 15 healthy volunteers for 7 days. A CCK-4 challenge was given before and after the 1-week treatment. A significant reduction in panic was found after the second CCK-4 challenge. A decrease in heart rate was also found to be significant after the tiagabine treatment; however, adrenocorticotropic hormone and cortisol levels did not change significantly. These small case series and panic induction studies suggest a potential antipanic effect of tiagabine. However, the effectiveness and tolerability of tiagabine in a clinical population must be determined with large-scale, controlled trials.

4.4 Carbamazepine

The use of carbamazepine in patients with panic disorder and benzodiazepine withdrawal has suggested that carbamazepine may have antipanic effects.[88] In an open-label trial by Tondo et al.,[89] 34 patients diagnosed with panic disorder with or without agoraphobia were treated with carbamazepine at a mean dose of 419 mg/day for 2–12 months. Patients' response was rated as 'absent/scarce' or 'good' based on a global rating of frequency of panic attacks, degree of avoidance behaviour and adaptive functioning. Using these criteria 20 patients (58%) were rated as having a 'good' response to the medication.[89]

However, in a controlled study of 14 patients with panic disorder by Uhde et al.,[90] carbamazepine was not found to be effective in treating panic disorder as carbamazepine treatment did not result in a significant change on any outcome measure. Forty percent of patients had a decrease in the frequency of panic attacks, 50% had an increase in frequency of panic attacks and 10% demonstrated no change. EEG abnormality or prominent psychosensory symptoms in this study did not predict response to carbamazepine.

4.5 Phenytoin

Phenytoin is used to control generalised tonic-clonic and psychomotor seizures. It appears to inhibit seizure activity through its action on the motor cortex. The antiepileptic effects of phenytoin likely come from its promotion of sodium efflux, thus stabilising firing thresholds against hyperexcitability.

McNamara and Fogel[91] reported three case reports of patients who experience a complete cessation of panic attacks as a result of treatment with phenytoin. These patients also had abnormal temporal lobe EEG patterns, comparable to interictal temporal lobe epilepsy. It is unclear whether these results can be applied to individuals with panic disorder as it is highly unusual for those patients to have EEG abnormalities.

5. Generalised Anxiety Disorder

Generalised anxiety disorder (GAD) is characterised by excessive, uncontrollable worry that has been present for at least 6 months. The anxiety and worry is centred on a number of day-to-day life events, including family life, work, health and finances, and is associated with feelings of restlessness, feeling 'on edge', being easily tired, poor

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concentration, irritability, muscle tension and sleep problems.[13]

A wide spectrum of drug classes have been shown to be efficacious in the treatment of GAD. Benzodiazepines have demonstrated safety and efficacy in more placebo-controlled trials than any other medication; however, rebound and withdrawal symptoms have limited their use.[92] Other, efficacious medications include the TCA imipramine,[93] buspirone,[94] as well as the SSRIs paroxetine[95] and sertraline,[96] and the SNRI venlafaxine.[97,98]

5.1 Gabapentin

Two cases have been reported documenting improvements in patients with GAD, following the addition of gabapentin to their treatment.[73] Improvements in both anxiety and arousal were noted.

5.2 Pregabalin

Pande et al.[99] compared the effectiveness and tolerability of pregabalin in treating GAD with that of lorazepam and a placebo. They randomly assigned 276 patients to four treatment groups for double-blind drug therapy of pregabalin (150 mg/day [n = 69] and 600 mg/day [n = 70]), lorazepam (6 mg/day [n = 68]) and a placebo (n = 69). Both the high-dose pregabalin and lorazepam groups demonstrated similar anxiolytic effects (based on HAM-A), which were significantly greater than placebo, as was low-dose pregabalin. Significant improvements from baseline to endpoint were found on the HAM-A for all active treatment groups. There were also significantly more responders (≥50% decrease in HAM-A) in the patient group receiving 600 mg/day of pregabalin (46%) and lorazepam (61%) then in those given placebo (27%). Although the adverse effects of pregabalin and lorazepam were similar, those in the pregabalin treatment group found the adverse effects more tolerable. The most common adverse effects for both treatment were dizziness (38.6% for pregabalin 600 mg/day and 13.2.3% for lorazepam 6 mg/day) and somnolence (35.7% for pregabalin 600 mg/day and 54.4% for lorazepam 6 mg/day). Only the lorazepam group demonstrated significantly more withdrawal effects than placebo.[99]

Lydiard et al.[100] combined data from five double-blind, placebo-controlled studies of GAD. Two studies compared the efficacy of pregabalin with that of alprazolam and placebo, one compared pregabalin with lorazepam and placebo, another compared pregabalin with venlafaxine and a placebo, and another compared pregabalin only with placebo. In their analysis the investigators found that pregabalin was significantly better at improving psychic and somatic anxiety symptoms than placebo at either 300 or 600 mg/day dosage. Compared with venlafaxine and alprazolam, pregabalin was associated with earlier (1-week) improvement. Pregabalin was associated with better improvements of the somatic factor of the HAM-A compared with venlafaxine.[100]

Montgomery et al.,[101] examining the same five studies, compared pregabalin with venlafaxine and alprazolam in terms of the speed of onset in treating GAD symptoms. All three treatments improved GAD symptoms; however, pregabalin and alprazolam demonstrated a more rapid treatment response.

In another analysis using data from the same five double-blind, placebo-controlled trials, Pollack et al.[102] evaluated the HAM-A scores of patients with low versus high baseline depression. Pregabalin treatment resulted in significant improvement as compared with placebo for all doses of pregabalin in both high and low baseline depression. Pregabalin at all doses was also associated with significant improvements in depressive symptoms versus placebo. Furthermore, pregabalin demonstrated equivalent efficacy in improving depressive symptoms compared with venlafaxine.[102] Comparing data from these five trials, venlafaxine had the highest rate of discontinuation due to adverse events at 20%, followed by the pregabalin 600 mg/day group at 16%.

The positive results of these large-scale, placebo-controlled trials of pregabalin in GAD make it a potentially promising new treatment. Further study of its ability to treat commonly comorbid symptoms, such as depressive symptoms, would allow for a better understanding of its role in treating GAD, whether as a first-line agent or a strategy reserved for treatment resistant cases.

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5.3 Tiagabine

Five patients with GAD and comorbid major depression and/or neuropathic pain were treated with tiagabine 6 mg/day which was generally well tolerated.[85] After 2 weeks of tiagabine treatment, a significant reduction in HAM-A score was found and was maintained for the 8-week treatment trial.

Similar findings were reported by Papp and Ray[103] using a mean dose of tiagabine 9 mg/day in the 8-week treatment trial of 25 patients with GAD. The number of patients rated as 'much' or 'very much' improved by CGI-I was seven (37%). In this trial, six patients withdrew because of adverse events, which included abnormal thinking, nausea, amnesia, anaemia, asthenia, colitis, diarrhoea, hallucinations, headache, migraine and somnolence. Rosenthal and Dolnak[104] conducted a 10-week, open-label, rater blinded study of 40 patients randomised to tiagabine or paroxetine. Tiagabine and paroxetine significantly reduced measures of anxiety and depression, along with improving sleep and overall functioning. Forty percent of the tiagabine group was considered responders (≥50% decrease in HAM-A), compared with 60% of the paroxetine group. In both groups 20% of patients achieved remission (HAM-A score ≤7). Both treatments were well tolerated with one patients withdrawing as a result of adverse events with tiagabine, and two patients with paroxetine.[104]

A recently completed double-blind, placebo-controlled trial has been presented examining tiagabine monotherapy (mean dose 10.5 mg/day) in GAD in which 272 patients were randomised to tiagabine or placebo for 8 weeks of treatment.[105] In those who completed the trial (n = 198) there was a significant reduction in the primary outcome measure (HAM-A); however, in ITT analysis the difference did not reach statistical significance. Fifty-seven percent of patients were considered responders ('much' or 'very much improved' on CGI-I) compared with 44% of the placebo group (p = 0.08). Tiagabine was generally well tolerated with dizziness, headache and nausea as the most common adverse events. Although tiagabine did not differ significantly from placebo in ITT analysis, the improvements seen in the observed cases indicate that tiagabine may reduce symptoms in GAD.[105]

Given these results, its seems tiagabine may have a significant anxiolytic effects in GAD. Further placebo-controlled and comparator trials are needed to determine the place of tiagabine in treating GAD.

5.4 Levetiracetam

One case report has been documented describing the use of levetiracetam in GAD. Levetiracetam was used adjunctively with citalopram to treat a 42-year-old female with GAD. Levetiracetam 250 mg/day was associated with reduced anxiety after 4 days with maintained improvements at 6 months.[106]

6. Obsessive-Compulsive Disorder

OCD is characterised by persistent, intrusive thoughts and/or images (obsessions) and repetitive, ritualistic behaviours that the individuals feel they must complete (compulsions).[13]

SSRIs are considered the gold standard treatment for OCD. Paroxetine,[107] fluoxetine,[108] citalopram,[109] fluvoxamine[110] and sertraline[111] have all demonstrated efficacy in placebo-controlled trials. Other agents which have demonstrated efficacy are clomipramine[112] and the MAOI phenelzine.[113] In treatment-resistant cases, placebo-controlled trials have supported the augmenting of an SSRI with haloperidol,[114] pindolol[115] or risperidone.[116] OCD is a chronic and disabling condition and, therefore, a continued search for treatment possibilities for refractory patients and partial responders is necessary.

6.1 Gabapentin

The use of gabapentin in the treatment of OCD has been reported by Cora-Locatelli et al.[117] in five patients who were partial responders to fluoxetine. Gabapentin (mean dose 2520 mg/day) and fluoxetine (mean dose 68 mg/day) were taken simultaneously for 6 weeks and were relatively well tolerated. All patients in the 6-week trial demonstrated improvements in anxiety, obsessive-compulsive symptoms, sleep and mood, based on clinical evaluations. However, it has been reported that these patients experienced a rebound of psychiatric symptoms once gabapentin was discontinued.[118]

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6.2 Valproic Acid

The use of valproic acid in treating OCD has been documented only in patients who have ceased treatment of conventional antiobsessional medications because of adverse effects such as anxiety, irritability, confusion, psychosis and other cognitive impairments.[119,120] Deltito[119] described the use of valproic acid in ten patients with OCD who discontinued the use of other medications, including clomipramine, fluoxetine, sertraline and paroxetine. Valproic acid was used as pre-treatment, with an initial dose of 250 mg/day and increased to a final dose of approximately 2500 mg/day. Treatment was then completed with the addition of typical antiobsessional pharmacotherapy without adverse effects. Successful outcomes, determined by clinical observations, were noted in eight of the ten patients. A case report by Cora-Locatelli et al.[120] also describes the use of valproic acid as pre-treatment in a patient in whom the adverse effects of fluoxetine were not tolerated. Fluoxetine was reintroduced and tolerated well; however, valproic acid was thought to be responsible for the improvements.

6.3 Carbamazepine

There are three reports documenting the use of carbamazepine in OCD. One case report described the improvement of a 27-year-old woman with OCD being treated as an inpatient with a combination of carbamazepine 500 mg/day and clomipramine 200 mg/day.[121] Previous psychopharmacological treatments were not effective, but the carbamazepine/clomipramine combinations resulted in significant improvements in anxiety, distress and habitual checking, and resulted in the patient being discharged from hospital. In an open-label trial involving four patients with OCD and temporal EEG abnormalities only one patient demonstrated improvement with carbamazepine.[122] In another series of nine patients treated with carbamazepine 400–1600 mg/day, only one of the eight patients who completed the trial demonstrated any improvement.[123] These preliminary finding suggest that carbamazepine is probably not an effective treatment for OCD; however, controlled investigations are needed to adequately evaluate its efficacy.

6.4 Topiramate

One open-label trial of topiramate augmentation to an SSRI in treatment-resistant OCD has been reported. Van Ameringen et al.[124] augmented treatment of 16 patients with topiramate (mean dose 253.1 mg/day) for 14–26 weeks. At endpoint 11 of 16 (68.8%) patients were considered responders (CGI-I rating of 'much' or 'very much improved'). A significant improvement on the CGI-S score was also found ($p < 0.001$). Most patients experienced one or more adverse events, which included weight loss, sedation/fatigue, paraesthesia and memory/word-finding problems.[124] These preliminary data may suggest a potential role for topiramate as an augmenting agent for treatment-resistant OCD, but further controlled trials are required to support this preliminary finding.

6.5 Lamotrigine

There is one report of lamotrigine treatment for OCD, in patients who did not respond to serotonin reuptake inhibitor (SRI) treatment. Eight patients with an inadequate response to at least 200 mg/day of sertraline or 225 mg/day of clomipramine for a mean period of 14 weeks had lamotrigine added for at least 4 weeks up to a maximum dose of 100 mg/day. The dose of SRI remained unchanged during the study period. No significant changes where found on the CGI-S or CGI-I scale. The mean baseline and endpoint Yale-Brown Obsessive-Compulsive Scale scores were 24.0 and 18.9, respectively.[125] This small trial of lamotrigine augmentation does not give an indication that this may be a useful strategy in refractory OCD. However, given the potential effect of topiramate, another agent with glutamatergic properties, further evaluation of lamotrigine is warranted using the higher doses that are found to be effective in treating bipolar depression.[126]

7. Mixed Anxiety Conditions

7.1 Tiagabine

In a case series of ten patients with an anxiety disorder or a comorbid anxiety condition, considered refractory to previous anxiolytic treatments,

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Table I. Summary of open-label and controlled trials of antiepileptic drugs in anxiety disorders

Disorder	Sample size	Design	Concomitant psychotropic medications	Outcomes	Adverse events	Reference
Valproic acid						
Social phobia	16	Open-label		All nonresponders	Sedation, headache, tremor, GI discomfort, weight gain	29
Social phobia	17	Open-label		41.1% responders by CGI-I	Nausea, somnolence, dizziness; fatigue	30
PTSD	16	Open-label	Antidepressants, benzodiazepines, antipsychotics	Decreased hyperarousal	GI symptoms	52
Combat-related PTSD	21	Open-label	Benzodiazepines	Symptom reduction in all three clusters	Rash, GI symptoms	53
Non-combat-related PTSD	10	Open-label		No improvements in PTSD or depressive symptoms		54
Panic disorder with/ without agoraphobia	10	Open-label		Significant reduction in CGI-S, HAM-D, Covi Anxiety Scale and SCL-90 panic factor	Nausea, dizziness, drowsiness, tremor, diarrhoea	80
Panic disorder	12	Open-label		Significant improvement based on CGI-S, CGI-I, HAM-A, BSI	Sedation, nausea, dry mouth	81
Panic disorder	16	Open-label		Significant reduction in HAM-A, 71% had decrease in frequency of attacks, 43% had complete remission		82
Panic disorder with comorbid mood instability	13	Open-label	Antidepressants, benzodiazepines, haloperidol	Decrease in panic frequency, HAM-A, BAI, BDI	Nausea, increased appetite	83
Panic disorder	12	Double-blind, placebo-controlled		Significant improvements on CGI-S and CGI-I scales	GI dysfunction, dizziness, somnolence	84
Gabapentin						
Social phobia	69	Double-blind, placebo-controlled		No significant difference in response (≥50% decrease on LSAS)	Dizziness, somnolence, nausea, flatulence, decreased libido	26
PTSD	30	Retrospective chart review	Antidepressants, antipsychotics, β-adrenoceptor antagonists, antiepileptics, benzodiazepines	77% of patients reported moderate or marked improvements in sleep duration	Sedation, mild dizziness	50
Panic disorder	103	Double-blind, placebo-controlled		No significant difference in response, significant improvement in PAS for severely ill	Headache, nausea somnolence	74

Continued next page

Table I. Contd

Disorder	Sample size	Design	Concomitant psychotropic medications	Outcomes	Adverse events	Reference
OCD	5	Open-label	Fluoxetine	Significant improvement in OCD, anxiety and mood symptoms as well as sleep		117
Pregabalin						
Social phobia	135	Double-blind, placebo-controlled		Significant decrease in LSAS in high-dose group (600 mg/day), significantly more responders in high-dose group than placebo	Somnolence	28
GAD	276	Double-blind, placebo-controlled		No significant difference between high-dose pregabalin (600 mg/day) and lorazepam on HAM-A, but both groups significantly greater than placebo	Somnolence, dizziness	99
GAD	1488	Data combined from five double-blind, placebo-controlled trials		All four doses of pregabalin improved HAM-A psychic and somatic symptoms		100
GAD	1488	Data combined from five double-blind, placebo controlled trials		Significant improvement on HAM-A, significantly early onset of action compared with venlafaxine		101
GAD	1488	Data combined from five double-blind, placebo controlled trials		Significant improvement on HAM-D, presence of subsyndromic depression has no effect on the anxiolytic response to pregabalin		102
Carbamazepine						
PTSD	10	Open-label		Decrease in intensity of nightmares, flashbacks and intrusive thoughts. 7/10 patients responded 'moderately' to 'very much' on CGI-I	Headache, tremor	58
PTSD	10	Open-label		Decrease in staff observation of violent behaviour and self report measures		59
Childhood PTSD	28	Open-label		22/28 patients free of PTSD symptoms		60
OCD with temporal EEG abnormalities	4	Open-label		1/4 patients demonstrated improvement		122
OCD	9	Open-label		1/8 patients who completed demonstrated improvement	Sedation	123

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Table I. Contd

Disorder	Sample size	Design	Concomitant psychotropic medications	Outcomes	Adverse events	Reference
Panic disorder with/ without agoraphobia	34	Open-label		58.8% patients rated as having a 'good response' by at least five independent investigators		89
Panic disorder	14	Controlled trial		40% had a complete cessation of panic attacks, 50% had an increase, 10% had no change	Restlessness, dizziness, blurred vision, rash	90
Topiramate						
Social phobia	23	Open-label		45.1% considered responders (CGI-I ≤2); 26.1% achieved remission (LSAS ≤30); significant decrease in LSAS	Weight loss, paraesthesia, headache	24
PTSD	35	Open-label	Antidepressants, antipsychotics, antiepileptic drugs, benzodiazepines, lithium	76% had reduced nightmares; 86% had reduced flashbacks, after 4 weeks 82% did not meet criteria for active PTSD	Urticaria, eating cessation, acute narrow-angle glaucoma, headache, memory difficulties	47
Tiagabine						
Treatment-refractory social phobia	14	Retrospective analysis, open-label	SSRIs, quetiapine, clonazepam, bupropion	64.2% (9/14) met response criteria (CGI-I ≤2); 35.7% (5/14) met remission criteria (LSAS ≤30)	Sedation, tiredness, headaches	34
Social phobia	51	Open-label		Significant reduction in LSAS and SPIN; 37% were responders (≥50% decrease in LSAS); 24% had remission (LSAS ≤30)		33
PTSD	6	Open-label	Antidepressants	Significant reduction in DTS		55
PTSD with comorbidity	7	Open-label	Antidepressants, valproic acid, benzodiazepines, buspirone	6/7 patients rated 'markedly improved' in CGI-C		129
PTSD	26	Open-label followed by randomisation to tiagabine or placebo		Significant reductions in open-label phase on all measures of PTSD, depression, general anxiety, social anxiety, resilience and disability and gains were maintained in both tiagabine and placebo group	Dizziness, dry mouth, nausea, headache	57
GAD	25	Open-label		Significant reduction in HAM-A, HAM-D and LSAS; 37% responded (CGI-I ≤2)	Somnolence, asthenia, abnormal thinking	103
GAD	40	Open-label, blind rater, positive controlled		Tiagabine and paroxetine significantly improved HAM-A scores and improved sleep quality	Headache, nausea, anorexia, dizziness	104

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Table I. Contd

Disorder	Sample size	Design	Concomitant psychotropic medications	Outcomes	Adverse events	Reference
GAD with comorbid MDD and/or neuropathic pain; panic disorder with/ without comorbidity	10	Open-label	Antidepressants, benzodiazepines,	Significant reduction in HAM-A	Nausea, dizziness, sedation	85
GAD	272	Double-blind, placebo-controlled		No significant difference in percentage of responders or HAM-A in ITT analysis; in completer analysis a significant reduction in HAM-A with tiagabine compared with placebo	Dizziness, headache, nausea	105
Panic disorder with/ without agoraphobia	4	Open-label		Reduction in anxiety, panic attacks, and agoraphobia in all four cases	Sedation, dizziness	86
GAD, PTSD, MDD, bipolar disorder, schizophrenia	10	Open-label	Risperidone, citalopram, paroxetine, clomipramine	All patients rated as 'much' or 'very much improved' on the CGI-C after 4 weeks		127
GAD, PTSD, panic disorder, social phobia	18	Open-label	SSRIs, SNRI, nefazodone, alprazolam	Significant improvements on HAM-A and BAI; 76% of patients were responders (≥50% decrease on HAM-A); 59% achieved remission (HAM-A ≤7)	Cognitive slowness, somnolence, headache	128
Lamotrigine						
PTSD	14	Double-blind, placebo-controlled trial		50% (5/10) patients of the lamotrigine group vs 25% (1/4) of placebo group rated as 'much' or 'very much improved' on the DGRP	Sweating, drowsiness, poor concentration	46
OCD	8	Open-label	Sertraline Clomipramine	No significant changes as rated by CGI-I scale		125
Levetiracetam						
Social phobia	20	Open-label		Significant reduction in LSAS, CGI-S, HAM-A and HAM-D	Drowsiness, nervousness	36
Vigabatrin						
PTSD	5	Open-label	Benzodiazepines	Amelioration of exaggerated startle response	Drowsiness	61

BAI = Beck Anxiety Inventory; **BDI** = Beck Depression Inventory; **BSI** = Brief Symptom Inventory; **CGI-C** = Clinical Global Impression of Change; **CGI-I** = Clinical Global Impression of Improvement; **CGI-S** = Clinical Global Impression of Severity; **DGRP** = Duke Global Rating Scale for PTSD; **DTS** = Davidson Trauma Scale; **GAD** = generalised anxiety disorder; **GI** = gastrointestinal; **HAM-A** = Hamilton Rating Scale for Anxiety; **HAM-D** = Hamilton Rating Scale for Depression; **ITT** = intention-to-treat; **LSAS** = Liebowitz Social Anxiety Scale; **MDD** = major depressive disorder; **OCD** = obsessive-compulsive disorder; **PAS** = Panic and Agoraphobia Scale; **PTSD** = Post-traumatic stress disorder; **SCL-90** = Symptom Checklist-90; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SPIN** = Social Phobia Inventory; **SSRI** = selective serotonin reuptake inhibitor.

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Table II. Levels of evidence for antiepileptic drug use in anxiety disorders[130]

Drug	Level of evidence[a]				
	panic disorder	OCD	PTSD	social phobia	GAD
Lamotrigine			2		
Topiramate			3	3	
Gabapentin	4	4	3	2	4
Pregabalin				2	2
Valproic acid	2	4	3	3	
Tiagabine	4		4		3
Carbamazepine	3	4	3		
Levetiracetam				3	4
Phenytoin	4				

a Level of evidence criteria: 1 = meta-analysis or replicated RCT that includes a placebo condition; 2 = at least one RCT with placebo or active comparison condition; 3 = uncontrolled trial with ≥10 subjects; 4 = anecdotal case reports.

GAD = generalised anxiety disorder; **OCD** = obsessive-compulsive disorder; **PTSD** = post-traumatic stress disorder; **RCT** = randomised controlled trial.

patients were given tiagabine as monotherapy (n = 5) or in combination with other medications (n = 5), including risperidone, citalopram, paroxetine and clomipramine.[127] Patients in the series had a primary diagnosis of GAD (n = 5), PTSD (n = 1), major depressive disorder (n = 2), bipolar disorder (n = 1) or schizophrenia (n = 1). All patients were rated as 'much improved' or 'very much improved' on CGI-C scale after 4 weeks, with most patients reporting marked improvement in anxiety after 1 week of tiagabine.

Schwartz et al.[128] conducted an 8-week open-label trial of tiagabine augmentation in a sample of mixed anxiety disorders, including GAD, panic disorder, PTSD and social phobia. Concomitant medications included SSRIs, venlafaxine, nefazodone and alprazolam. Significant improvements at baseline in anxiety were found as measured by the HAM-A and the Beck Anxiety Inventory. At endpoint 76% of patients were considered responders (≥50% reduction in HAM-A) and 59% achieved remission (HAM-A total score ≤7).

These open-label trials of tiagabine in mixed anxiety disorders may give an indication of potential anxiolytic effects of tiagabine. However, the inclusion of multiple anxiety diagnoses and multiple concomitant medications significantly limit the conclusions that can be drawn from them. Placebo-controlled trials examining the efficacy of tiagabine as monotherapy and augmentation trials in individual anxiety disorders would help us determine the role this agent may play in the treatment of anxiety conditions.

8. Conclusion

The psychotropic use of antiepileptic drugs is an active area of research, with a number of case reports, case series and open-label trials suggesting the potential efficacy of these treatments in a variety of disorders (table I). However, the strongest evidence is from controlled studies (level 2 evidence) and would suggest the efficacy of lamotrigine in PTSD, gabapentin in social phobia, pregabalin in social phobia, GAD with/without comorbidity and valproic acid in panic disorder (table II).

In spite of level 2 evidence criterion being met for the use of lamotrigine in PTSD and valproic acid in panic disorder, these results need to be viewed with caution given the very small sample sizes used in these studies. The remainder of the evidence for the antiepileptic drugs remains at level 3 or 4. Although there have been numerous studies and reports describing the use of antiepileptic drugs in anxiety disorders, they have suffered from a number of methodological problems, including inadequate sample size, lack of placebo controls, heterogeneous patients samples, use of inadequate dosages of medication, lack of controlling for patient variables such as comorbidity, subtype of disorder and use of concomitant medications, as well as the reliance on impressionistic outcome measures such as the CGI.

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Although the antiepileptic drugs seem to be promising treatments for anxiety disorders, it is not yet clear where their place will be in the spectrum of treatments available in anxiety disorders. Given the very preliminary data on the efficacy of antiepileptic drugs in anxiety disorders, their current clinical use should be reserved for treatment refractory individuals, as augmentation strategies for partial responders and alternative treatment for those individuals who cannot tolerate first-line treatments such as the SSRIs. There is currently no evidence to support the use of antiepileptic drugs as first-line treatments. However, for the antiepileptic drugs that have thus far shown some evidence of benefit in the treatment of anxiety disorders, their potential use in combination with mood stabilisers in bipolar disorder patients who have a comorbid anxiety disorder may be considered.

Future research examining the potential use of antiepileptic drugs in anxiety disorders will require large-scale, controlled trials in a number of the anxiety disorders, head-to-head comparisons with first-line treatments, as well as an examination of clinical subgroups that may preferentially respond to these drugs. In addition, it may be warranted to evaluate the potential use of antiepileptic drugs in youth with anxiety disorders, given the current concerns about the safety and efficacy of SSRIs in this age group.

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