Antiepileptic Drugs for the Treatment of Post-traumatic Stress Disorder

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Post-traumatic stress disorder (PTSD) is a disruptive, chronic, and relatively common disorder that is often difficult to treat. Many patients with PTSD are unresponsive, have only moderate or marginal responses, or have troubling side effects to first-line serotonin reuptake inhibitor treatment. Studies suggest that antiepileptic drugs (AEDs) may be an effective treatment alternative or adjunctive treatment for the symptoms of PTSD. Recent results from case reports and open and controlled studies on the efficacy and tolerability of AEDs in PTSD are reviewed here, and their methodological limitations are discussed when relevant. AEDs shown to be effective in double-blind, placebo-controlled trials of PTSD include lamotrigine, topiramate, and tiagabine. Other AEDs that appear promising in open-label trials of PTSD include carbamazepine, valproate, gabapentin, vigabatrin, phenytoin, and levetiracetam. Stress-activated limbic kindling may be involved in the pathogenesis of PTSD. The possibility that AEDs may be effective in the treatment of PTSD due to their antikindling effect is discussed, and suggestions for future research are made.

Introduction

Post-traumatic stress disorder (PTSD) is a pathologic response to a witnessed or experienced traumatic event in which a person responded with intense fear, horror, or helplessness [1]. PTSD is common, yet it is difficult to treat and is associated with interpersonal and/or occupational distress and significant mortality, morbidity, and burden to society. This often-chronic condition is characterized by three symptom clusters, according to the *DSM IV*: 1) intrusive (re-experiencing the trauma via persistent and intrusive memories, recurrent nightmares, and flashbacks/reliving), 2) avoidance/numbing (avoiding thoughts, feelings, activities, and stimuli associated with the traumatic event; amnesia; diminished responsiveness to the external world; and reduced ability to feel emotions), and 3) hyperarousal (insomnia, poor concentration, exaggerated startle response, irritability, and anger) [1]. Severe trauma affects approximately one third of the population [2], and approximately 15% to 24% of those affected will develop PTSD [3,4]. There is an approximate 8% lifetime prevalence for PTSD in the US adult population [1], and most studies report a 2:1 female-to-male ratio of lifetime prevalence [3,4]. There is evidence of a heritable component to PTSD, and a history of depression in first-degree relatives has been associated with increased vulnerability to the development of PTSD. PTSD has a variable course. Approximately 50% of patients completely recover within 3 months [1]; however, symptoms remain for more than 10 years after the trauma in approximately one third of patients [5].

Selective serotonin reuptake inhibitors (SSRIs) are established as first-line pharmacotherapy for PTSD [6–8]. In fact, the only drugs approved by the US Food and Drug Administration (FDA) to treat PTSD are the SSRIs sertraline and paroxetine. However, many patients are unresponsive to these drugs or have only moderate or marginal responses or have troubling side effects [9]. Clinical response to antidepressants in treatment of PTSD is usually modest (effect sizes > 1.0) [10]. Thus, the utility of other drugs should be explored. Reports suggest that antiepileptic drugs (AEDs) may be an effective treatment alternative for PTSD [5,11]. AEDs shown to be effective in double-blind, placebo-controlled PTSD trials include lamotrigine [12], topiramate [13••], and tiagabine [14••]. Other AEDs that appear promising in open-label trials of PTSD include carbamazepine (CBZ), valproate (VPA), gabapentin, vigabatrin, levetiracetam, and phenytoin. In a review, Davis et al. [15•] conclude that in addition to SSRIs, long-term treatment with atypical antipsychotics (risperidone, clozapine), non-SSRI antidepressants (nefazodone), and AEDs (VPA) also results in significant PTSD symptom improvement.

The hypothalamic-pituitary-adrenal axis; noradrenergic, serotonergic, dopaminergic, and sympathetic systems; endogenous opiates; γ-aminobutyric acid (GABA); N-methyl-D-aspartate (NMDA); and cortico-releasing

factors have been implicated in the neurobiology of PTSD [16,17]. Brain areas involved in PTSD include the locus coeruleus, prefrontal cortex, cingulate, hippocampus, and amygdala [16,17]. PTSD symptoms suggest hyperreactivity and hyperarousal of the sympathetic nervous system. Thus, transmission of GABA, an inhibitory neurotransmitter, is potentially abnormal in PTSD patients. Drugs that modulate GABA, often used adjunctively, have shown promise in treating anxiety disorders [18].

Kindling model of PTSD

Stress-activated limbic kindling may be involved in the pathophysiology of PTSD [19–21]. In kindling, repeated stimulation in the hippocampus or amygdala leads to an enhancement of the postsynaptic potential and an increased risk of seizures. The kindling model of epilepsy applied to PTSD states that repeated trauma, such as childhood abuse, followed by recurrent intrusive memories may kindle limbic nuclei, leading to some of the behavioral changes seen in PTSD (eg, the all-or-none reactions). Neuronal changes in the limbic system may occur after exposure to trauma and produce a lowered arousal threshold that leads to the re-experiencing of symptoms [22]. Memories of the traumatic event may repeatedly stimulate the hippocampus and amygdala (kindling) and thus alter multiple biological systems, including GABA pathways, and eventually lead to PTSD [23]. PTSD patients may become sensitized [24] so that prior exposure of the amygdala to a single high-intensity stimulus may result in the eliciting of responses to subsequent low-intensity stimuli. In fact, a functional MRI study showed increased reactivity of the amygdala in a group of PTSD patients [25].

The hypothesis that exposure to traumatic events may sensitize or kindle limbic nuclei has led to efforts to treat PTSD with AEDs, as they are thought to work in part via an antikindling effect [21]. GABA receptor agonists block sensitization in animals [24], and AEDs such as CBZ, VPA, gabapentin, and topiramate increase GABA levels in the human brain [26]. The AED phenytoin also has been shown to decrease seizures in kindled animals [27]. Some of the hyperarousal symptoms in PTSD, such as irritability and anger outbursts, occur frequently in epilepsy [28], and AEDs have been shown to alleviate these symptoms in epileptic and nonepileptic disorders [29]. AEDs also have been effective in bipolar disorder (possibly via antikindling effects) and in reducing aggression in chronic psychiatric patients [30]. Several reports suggest that AEDs may ameliorate PTSD symptoms [5], especially increased arousal and intrusive re-experiencing [19]. AEDs may be effective in PTSD due to their antikindling or threshold-elevating effects [5], which may occur via inhibition of NMDA receptors and enhancement of GABA release [31]. The most recent evidence on the efficacy and tolerability of AEDs for the treatment of PTSD is reviewed here.

Lamotrigine

Lamotrigine has a range of mechanisms of action [32], which may explain its efficacy in a variety of neurological and psychiatric disorders. Lamotrigine has been shown to block voltage-sensitive sodium (Na^+) channels [33], inhibit glutamate release [34], inhibit the reuptake of serotonin and acetylcholine, and affect GABA neurotransmission [34–36], which may explain its reported utility in PTSD [12,33]. Outside the first-line monotherapy treatments (SSRIs), adjunctive use of lamotrigine may be a potential treatment option for PTSD. Hertzberg et al. [12] conducted the first controlled study of an AED in PTSD and the only study of lamotrigine for the treatment of PTSD to date. In this 12-week, double-blind, placebo-controlled study, patients were randomized to lamotrigine or placebo after an initial drug-free period. Fifty percent (five of 10) of patients who received lamotrigine responded as "much improved" or "very much improved" on the Duke Global Rating for PTSD, compared with 25% (one of four) who received placebo. In particular, lamotrigine patients' avoidance/numbing and re-experiencing (ie, nightmares, flashbacks) symptoms improved compared with the placebo group. Both men and women, as well as those exposed to combat-related and civilian traumas responded to lamotrigine, which was generally well tolerated. Additional double-blind, placebo-controlled studies with larger samples are needed to further assess the efficacy of lamotrigine as monotherapy or as an adjunct to antidepressants for PTSD.

Topiramate

The newer AED topiramate has been used for psychiatric illnesses because, among other things, it is associated with decreased impulsivity, aggression, and weight [37]. It works via a variety of mechanisms, including Na^+ channel blockade [38], enhanced GABA transmission [39], glutamate inhibition [40], and inhibition of some voltage-activated Ca^{2+} channels [41]. As topiramate has been shown to inhibit kindling in animals [42,43], it may be effective in treating PTSD. Topiramate attenuated exaggerated acoustic startle in an animal model of PTSD [44] and thus may treat trauma-enhanced acoustic startle response in humans, a prominent PTSD symptom for which there are few treatments.

Aalbersberg and Mulder [45] report two PTSD patients who were successfully treated with topiramate, which acted rapidly at a relatively low dose. Re-experiencing of traumatic events and nightmares was particularly responsive. This coincides with one case study and two open-label studies suggesting efficacy of topiramate for treating nightmares and insomnia in PTSD [46,47]. Further, topiramate reduced and even eliminated trauma-related intrusive memories and nightmares and normalized depressed mood in three treatment-refractory chronic PTSD patients [46]. In an open-label study, Berlant [48]

treated 24 chronic and treatment-resistant PTSD patients with topiramate added to existing medication. According to self-report, nightmares were suppressed in 88% of patients (11 of 16 fully, three of 16 partially). Globally, of the 24 patients, 17 (71%) reported a full response, five (21%) had a partial response, and two dropped out with no response. The nonhallucinatory subgroup (n = 18) had an even higher response rate (94%), and all complete responders belonged to this subgroup.

Another open-label trial reviewed medical records of civilian, adult, chronic PTSD outpatients [47]. Based on endpoint (mean of 33 weeks) self-reports, topiramate as add-on therapy (n = 28) or monotherapy (n = 7) was effective for PTSD symptoms, was well tolerated, and had a rapid onset of action. Response was seen at low doses compared with those used in other psychiatric disorders [49]. However, only one half of the sample (n = 17) completed a standardized self-report PTSD measure (the PTSD Checklist-Civilian Version [PCL-C]), which was only completed at baseline and at 4 weeks. Also, the patient sample was heterogeneous with different PTSD subtypes (hallucinatory and nonhallucinatory), significant comorbidity (eg, bipolar disorder), and both monotherapy and adjunctive therapy.

In a prospective, open-label, 12-week study, adult civilian outpatients with nonhallucinatory, chronic PTSD received topiramate as augmentation (n = 28) or monotherapy (n = 5) [50•]. Topiramate improved re-experiencing, avoidance, and hyperarousal symptoms by 49% in those who took the PCL-C at baseline and at week 4 (n = 30) and decreased intrusions and nightmares in 94% and 79%, respectively, of patients with these symptoms. These promising findings converge with those of previous open-label studies [47,48]. But again, there was no structured assessment after week 4, and the sample was heterogeneous (eg, high comorbidity). In the only placebo-controlled, double-blind trial to date, Tucker et al. [13••] assessed topiramate monotherapy for 12 weeks in non–combat-related PTSD adult outpatients. Compared with placebo (n = 19), topiramate patients (n = 19) had a nonsignificant decrease in total Clinician-Administered PTSD Scale (CAPS) score and Clinical Global Impressions-Improvement Scale (CGI-I) scores and significantly reduced re-experiencing symptoms (CAPS cluster B) and treatment outcome PTSD scale scores.

Adequately powered placebo-controlled trials of topiramate as monotherapy or adjunctive therapy for PTSD are needed, especially in more homogeneous samples with less comorbidity. Topiramate does not appear to be associated with the weight gain or hematologic, pancreatic, cardiac, and hepatic toxicity seen with VPA or CBZ [5]. Topiramate also is relatively free of the common SSRI side effects such as weight gain, sexual dysfunction, or sedation, and it does not appear to destabilize mood in those with comorbid bipolar disorder. However, depression (~ 15% of trials [51]) and psychotic symptoms reportedly have emerged in some epileptic patients treated with topiramate.

Gabapentin

The novel AED gabapentin, which is structurally similar to GABA, appears to have anxiolytic properties [52] and potential as a treatment for behavioral dyscontrol [53] and bipolar disorder [54,55]. Gabapentin has few drug interactions, hepatic complications, or risks of addiction, and it is well tolerated, but side effects include fatigue, drowsiness, dizziness, and ataxia [56]. Gabapentin's mechanism of action is unclear, but in epileptic patients, it has been shown to increase brain levels of GABA [57], an inhibitory neurotransmitter important for controlling aggressive behavior [58] and decreasing stress or anxiety [59]. Exaggerated norepinephrine system responsivity has been shown in PTSD and may contribute to its core symptoms, such as sleep disturbances [60]. Increased GABA may decrease locus coeruleus firing and subsequent norepinephrine release, resulting in reduced PTSD symptoms [61].

Sleep disturbance symptoms of PTSD such as insomnia and nightmares often are refractory to antidepressants. As gabapentin increases slow-wave sleep [62], Hamner et al. [61] reviewed records of 30 PTSD patients treated with adjunctive gabapentin for 1 to 36 months. Moderate or marked improvement in sleep duration was reported in 77% of patients, and most also had decreased nightmare frequency. However, this was a retrospective study, most patients had comorbid major depressive disorder (67%) and were on antidepressants (83%), and a standard PTSD rating scale was not used. Case reports also have described the successful treatment of PTSD with gabapentin [63–65], and gabapentin reduced cocaine cravings in a man aged 41 years with cocaine abuse and PTSD who abused gabapentin (up to 1500 mg/d for 3 months), but its effect on his PTSD symptoms was not mentioned [66]. Despite their limitations, the preliminary findings suggest that gabapentin may be useful for chronic PTSD, especially sleep disturbance and nightmare symptoms. Prospective, double-blind, placebo-controlled trials are needed to further define gabapentin's utility in the treatment of PTSD.

Valproic Acid (VA)

Introduced in 1967, divalproex sodium (DVP), or VA or VPA, is FDA approved for use as an AED and mood stabilizer. VA has been widely used in various psychiatric populations [30,37] due in part to its relatively low toxicity. Drugs that interfere with kindling, which is thought to underline nightmares, flashbacks, and hyperarousal, have been shown to reduce hyperreactivity and hyperarousal in Vietnam veterans with PTSD [67]. VA interferes with kindling in part by increasing GABA levels and GABA receptor site sensitivity in the limbic system and thus may reduce PTSD symptoms such as intrusions or hyperarousal [22,68]. VA also enhances serotonin function, which may improve mood and anxiety symptoms [69]. A US military report [70] recommended VA as an alternative drug for treatment of PTSD, especially in

treatment-resistant patients (most improved in 3–5 days). In a chart review of PTSD veterans treated with DVP, 25 patients (50%) were rated as "much improved" or "very much improved" on the CGI-I by a blinded investigator [71•]. VA also has been effective in treatment of PTSD in case studies [72–74], and repeated VPA administration improved behavioral disturbances in a mouse model of PTSD [75••].

In a 1-year, open-label VPA trial, 10 of 16 Vietnam veterans with combat-related PTSD improved significantly, especially in hyperarousal/hyperreactivity and avoidant symptoms [19]. But there was little improvement in their intrusive and re-experiencing symptoms. However, this study was not placebo controlled; timepoints of evaluation were not specified; psychotropic medications were continued; and again, standardized PTSD rating scales were not used. In another open-label trial, Clark et al. [76] used standardized rating scales at baseline and at 8 weeks to investigate DVP in 16 male PTSD combat veterans (three dropouts due to side effects). Hamilton Rating Scale for Anxiety (HAM-A) and for Depression (HAM-D) scores significantly decreased, as did intrusion and hyperarousal symptoms (CAPS), but avoidance/numbing symptoms did not. These results are contrary to those of Fesler [19], who found that VA decreased avoidance symptoms, but not intrusive symptoms, in combat-related PTSD. Differences in assessment measures or length of follow-up (longer in Fesler [19]) may explain these discrepancies [5].

Both of the previously mentioned open-label studies [19,76] allowed use of concomitant psychotropic medications. In a subsequent open-label study, Petty et al. [77] were the first to investigate DVP as a monotherapy for PTSD. Unlike Fesler [19], Petty et al. [77] used standardized rating scales in this 8-week trial of 30 combat-induced PTSD veterans (most were treatment refractory; 19 had current major depressive disorder). VPA significantly decreased all three PTSD symptom clusters and improved HAM-A and HAM-D scores. Most improved by week 4. Limitations of this study include its open-label design, allowance of sleep medications, and high comorbidity and dropout rate (16 dropouts).

The three open trials [19,76,77] discussed thus far report beneficial effects of VA as adjunctive or monotherapy for PTSD. But these studies were only conducted in male veterans with combat-related PTSD, and approximately one half continued to take their previous psychotropic medication. Otte et al. [78•] conducted the first open-label trial of VA as monotherapy for men and women with non–combat-related chronic PTSD (n = 10). In contrast to earlier open studies that reported the efficacy of VPA in male veterans with chronic combat-related PTSD [19,76,77], VA was not effective for non–combat-related PTSD or depressive symptoms in this 8-week trial using standardized scales. VA has been shown to elicit mood-stabilizing and antiaggressive properties [69], which may explain its efficacy in male combat-related PTSD veterans, who may suffer from aggression and irritability more than civilian and female patients. Another factor contributing to these negative findings may be the low plasma concentration of VA at endpoint (mean = 62 μg/mL) compared with the earlier studies (69–80 μg/mL) and therapeutic concentrations (50–100 μg/mL). Other limitations of this study include its open-label design, small sample size, high comorbidity (six had current major depression), and dropout rate (two discontinued due to alcohol relapse and noncompliance, three due to side effects). However, the earlier studies [19,76,77] also reported high rates of attrition (22%–53%).

In a 12-week, double-blind, placebo-controlled study of DVP in the treatment of impulsive aggression in patients with cluster B personality disorder (n = 96), intermittent explosive disorder (IED) (n = 116), or PTSD (n = 34), no treatment effect was observed when all diagnostic groups were combined [79]. However, DVP was superior to placebo in the treatment of impulsive aggression, irritability, and global severity in the cluster B personality disorder subgroup. Cluster B patients may have had greater lifetime histories of aggression and thus may be more responsive to DVP than IED and PTSD patients [80]. Further, DVP may exert its effect on the affective instability symptom domain of cluster B patients, who may have neurobiological features similar to those of bipolar spectrum patients, who tend to respond to DVP [29]. Interpretation of results in the PTSD subgroup was limited by the small sample size, and patients were selected for aggressive behaviors and not classic PTSD symptoms.

Data obtained thus far suggest that VA may be useful in treatment of PTSD; however, there are conflicting reports regarding its efficacy in treating all the core symptoms of PTSD and in different genders and types of trauma. Therefore, controlled trials are needed to further study the efficacy of VA in PTSD.

Tiagabine

The novel selective GABA reuptake inhibitor (SGRI) tiagabine increases extracellular GABA levels [81]. It is FDA approved for the treatment of certain forms of epilepsy and is currently the only SGRI available in the United States. It also has been used as a mood stabilizer and in treatment of panic disorder. Tiagabine has exhibited antikindling and antianxiety effects in preclinical studies [82,83], and its anxiolytic effects have been shown across anxiety disorders [84,85•]. Tiagabine is well tolerated and may hold promise in treating PTSD via its facilitation of GABA neurotransmission [23,86,87]. In fact, tiagabine has shown potential as augmentation or monotherapy for PTSD in preliminary human studies [87,88] and has been shown to improve sleep quality in people with generalized anxiety disorder [89], as well as insomnia and nightmares in PTSD [23]. In an 8-week, open-label study for treatment-resistant anxiety (four of 25 patients had PTSD), tiagabine augmentation reduced anxiety, improved sleep

quality, and was well tolerated [19]. Further, tiagabine reduced PTSD symptoms and was well tolerated in several case reports [87,90].

An open-label case series of six PTSD patients (all had a comorbid mood disorder) examined tiagabine augmentation to antidepressant treatment [91]. Anxiety was significantly reduced at week 1, and the reduction was maintained at week 6. Aggression also was significantly reduced. In another open-label case series, tiagabine augmentation significantly improved PTSD symptoms within 2 weeks (maintained at 8 weeks) in six of seven women with PTSD [23]. The first double-blind study of tiagabine for PTSD used a two-phase design (12 weeks each) [14••]. Significant improvement was seen on all outcome measures, and tiagabine was well tolerated in the 19 (of 26) adult PTSD outpatients who completed the phase I open-label trial. In the double-blind phase, phase I responders (minimal CGI-I improvement, n = 18) were randomized to tiagabine (continued on same dose) or placebo (tapered off tiagabine as they changed to placebo). Improvements with tiagabine were upheld across all efficacy measures, and the tiagabine group trended toward greater likelihood of remission, but the tiagabine group's incidence of relapse was not less than that of the placebo group.

However, as opposed to civilian case studies [23,87,90] and the two-phase study discussed previously [14••], tiagabine (n = 116) did not differ significantly from placebo (n = 116) on any outcome measures, which included structured standardized scales, in a recent 12-week, double-blind study of adults with PTSD [92••]. One explanation for these negative findings is that certain populations with different types of trauma may be less responsive to medication than others. Also, it is unclear whether tiagabine did not separate from placebo due to a type II error, or if tiagabine was simply ineffective. Drugs with proven efficacy in PTSD, such as SSRIs, have failed to separate from placebo in a number of cases [92••]. The lack of a significant drug effect also may have been due to the high placebo response rate (54%), which is comparable to rates reported in previous placebo-controlled PTSD trials (38%–62%) [6,7].

These preliminary findings suggest that tiagabine may be a promising treatment option for PTSD. Large, randomized, double-blind, placebo-controlled studies are needed to assess tiagabine's potential in the treatment of PTSD. Because of its lack of sedation, memory and reaction time impairment, and potential for dependence and withdrawal, tiagabine may be a potential alternative to benzodiazepine augmentation in PTSD patients. It also may be safer than other AEDs (CBZ, DVP, topiramate) that are used off label to treat anxiety, which require blood and/or observational monitoring [90].

CBZ

CBZ's main mechanism of action is voltage-gated Na^+ channel blockade, which prevents the release of excitatory neurotransmitters. CBZ is indicated for the treatment of epilepsy and bipolar disorder. In the 1980s, CBZ became of interest in treating impulsive aggression in psychiatric disorders because of its efficacy in treating epileptic patients with aggressive outbursts and irritability [37]. CBZ can reduce noradrenergic arousal, induce a hypnotic effect, and decrease sleep latency. It also interferes with/reduces limbic kindling, which may explain its efficacy in treating mania, agitation, and impulsivity [30,68], and suggests that it may be useful in PTSD. In fact, CBZ efficacy for PTSD has been described in several case reports [74,93,94] and small series [95–97], but without using standardized PTSD scales. Open-label PTSD trials, conducted mainly in treatment-resistant combat veterans, show that both CBZ [95,96] and VPA [19] improve hyperarousal/hyperreactivity symptoms such as insomnia, irritability, and angry outburst. However, CBZ also may reduce re-experiencing/intrusive symptoms [95,98], whereas VA may reduce avoidance/numbing but not re-experiencing symptoms [69].

Several open-label studies suggest that CBZ may be useful for the treatment of PTSD. After a 5-week, open-label CBZ trial, seven of 10 combat veterans with PTSD and a comorbid personality disorder were rated as "moderately" or "very much" improved on the CGI-I [95]. The frequency and intensity of their nightmares, flashbacks, and intrusive thoughts were reduced as measured by self-report and interview-rated scales. CBZ's efficacy, especially for intrusive symptoms, may have been mediated by its antikindling effects. Wolf et al. [96] reported significant decreases of impulsivity, violent behavior, and angry outbursts in eight male PTSD Vietnam veterans treated with CBZ, but standardized scales were not used. Looff et al. [97] administered CBZ to sexually abused child/adolescent PTSD inpatients for 17 to 92 days. PTSD symptoms were eliminated in 22 of 28 patients and significantly improved in the remaining six patients. But, again, no standardized measures were used, more than one half had a comorbid *DSM IV* disorder, and the placebo effect and clinician bias could not be ruled out in this open-label study. Finally, CBZ was effective for treatment of PTSD (maximum dose 800 mg) in a large, retrospective study of US military veterans (n = 632) [70].

When prescribing CBZ, clinicians should take into account possible drug interactions; side effects, especially blood dyscrasias and hepatotoxicity [29]; and the need for therapeutic drug monitoring [99]. Double-blind, placebo-controlled trials are needed to fully determine the efficacy of CBZ in PTSD.

Oxcarbazepine (OXC)

The newer AED OXC, FDA approved in the United States in 1999, is used as a monotherapy and adjunctive therapy for partial seizures in adults and children [100]. Its primary mechanism of action is thought to be voltage-dependent Na^+ channel blockage [100]. OXC is structurally related

to CBZ but not metabolized by 10,11-epoxide, which may decrease its incidence of adverse effects [101]. OXC has been shown to be better tolerated than and as effective as CBZ in epileptic patients [101] and has several advantages over CBZ. It does not induce its own metabolism, has limited drug interactions, is not associated with serious blood dyscrasias, and does not require frequent blood plasma monitoring [100]. However, hyponatremia has been associated with OXC [100], so serum sodium may need periodic monitoring. Common OXC side effects appear to be dosage related and include dizziness, drowsiness, vomiting, and nausea [102].

As OXC is a keto analogue of CBZ, and CBZ had been reported to improve PTSD symptoms, OXC also may reduce PTSD symptoms. There have been only two reports on the beneficial effects of OXC in treatment of PTSD to date. Berigan [103] described improvements in PTSD symptoms with OXC augmentation (300 mg/d titrated to 900 mg/d) that were maintained at 4-month follow-up in a man aged 46 years with chronic PTSD who was intolerant or unresponsive to multiple drugs, including CBZ and VA. Further, a woman aged 38 years with chronic PTSD and concurrent bipolar disorder who partially responded to CBZ had significant improvement in her PTSD and mood symptoms and no side effects with OXC monotherapy up to 1500 mg/d [104]. Controlled studies are needed to investigate the use of OXC for treatment of PTSD. Also, as bipolar disorder is common in PTSD patients [4], studies of OXC in PTSD patients with comorbid bipolar disorder are warranted.

Other AEDs

Vigabatrin, a well-tolerated specific GABA transaminase inhibitor, is used as an AED [105] and to treat startle disease in neonates [106]. In a series of five chronic PTSD patients with prominent hypervigilance/startle, vigabatrin augmentation at low doses (250–500 mg/d) resulted in rapid improvement of their exaggerated startle responses and had a general calming effect [107]. Vigabatrin was well tolerated and did not produce the side effects common to benzodiazepines (sedation and dependency). Thus, vigabatrin may be a useful alternative to benzodiazepines to block startle response and as an adjunctive anxiolytic for the treatment of PTSD. Further clinical trials are needed.

Phenytoin, used to treat epilepsy, is thought to modulate glutamatergic transmission. PTSD may involve altered glutamatergic transmission leading to neurotoxicity, especially in the hippocampus, which may be treated with phenytoin. In an open-label pilot study, nine adults (four males) with combat- or civilian-related PTSD received phenytoin for 3 months [108•]. PTSD symptoms decreased significantly in each symptom cluster, but anxiety and depression severity did not. Subjects also underwent MRI and neuropsychological testing [109•]. Right brain volume increased significantly by 6% after administration of phenytoin. Cognition and memory improvements were not significant, but increased hippocampal volume correlated with improved executive function and reduced symptom severity. Thus, phenytoin may be effective in treating PTSD via its antiglutamatergic effects and associated brain structure changes. Phenytoin also has been shown to prevent stress-induced hippocampal damage in rats [110] and thus may prevent such stress-induced damage to the human brain and possibly prevent PTSD onset [5]. Double-blind, controlled, randomized studies are needed to further examine phenytoin's efficacy for PTSD.

Preliminary evidence suggests that the novel AED levetiracetam, FDA approved as an adjunctive treatment for partial-complex seizures, may have efficacy in psychiatric disorders characterized by affective lability, impulsivity, and anxiety [37]. Kinrys et al. [111••] conducted the only known study of levetiracetam for the treatment of PTSD. In this retrospective study, 23 PTSD patients who were partial responders or nonresponders to antidepressants received levetiracetam for 9.7 ± 3.7 weeks. Patients improved significantly on all outcome measures, and at endpoint, 13 patients (56%) met responder criteria, and six (26%) met remission criteria. No one discontinued due to side effects, and adverse events were mild. Thus, levetiracetam may be effective in conjunction with antidepressants for treatment-resistant PTSD.

Conclusions

The current first-line SSRI treatments of PTSD are not fully effective, and side effects limit their use. Treatment with AEDs may be an attractive alternative, with a number of case reports; case series; and open-label and double-blind, placebo-controlled trials suggesting the potential efficacy of AEDs for treatment of PTSD. However, these results should be viewed cautiously given the limitations of some studies, such as small sample sizes; lack of placebo controls; heterogeneous patient samples; use of inadequate drug doses; lack of controlling variables such as comorbidity, disorder subtype, and concomitant medication use; lack of standardized rating scales; and/or reliance on impressionistic outcome measures (eg, CGI). As the data on the efficacy of AEDs in PTSD are still preliminary, use of AEDs should be reserved for treatment-refractory patients, as an augmentation for partial responders, or as an alternative treatment for those intolerant to first-line SSRIs. Currently, there is no evidence to support the use of AEDs as first-line treatment. However, the new AEDs may be useful for combination therapies, particularly in refractory PTSD. A combination of AEDs and antidepressants may cover the wide spectrum of PTSD symptoms and may help patients with comorbid bipolar disorder [85•].

Long-term and large-scale controlled trials, using standardized scales, in both men and women with both combat- and non–combat-related trauma are needed

to better define the role of AEDs as monotherapy and adjunctive therapy for PTSD. Future research will require comparisons with first-line treatments, combination treatment in refractory PTSD patients, and an examination of subgroups that may preferentially respond to AEDs. Further, given the current safety and efficacy concerns about SSRIs in children and adolescents and the limited psychopharmacologic data concerning PTSD in this population, future studies should explore the use of AEDs for treatment of PTSD in this age group. Brain imaging also could be used to better target drug responsivity, and regional transcranial magnetic stimulation could be explored as a possible treatment for PTSD [5]. In sum, alternative medications such as AEDs may help to relieve the symptoms of PTSD, a disruptive, chronic, and relatively common disorder that is often difficult to treat.

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