Treatment of Posttraumatic Stress Disorder With Phenytoin: An Open-Label Pilot Study

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Background: Phenytoin is an anticonvulsant used in the treatment of epilepsy. Its mechanism of action is incompletely understood but most likely involves modulation of glutamatergic transmission. The neurobiology of posttraumatic stress disorder (PTSD) has been hypothesized to involve, at least in part, alterations in glutamatergic transmission in the hippocampus and possibly other brain regions. The purpose of this study was to assess the effects of phenytoin on symptoms of PTSD.

Method: Phenytoin was administered in an open-label fashion for 3 months to 9 adult male and female patients with DSM-IV PTSD related to a variety of traumas including childhood abuse, combat, and car accidents. Dosage was adjusted to maintain the therapeutic blood levels used in the treatment of epilepsy. Subjects were assessed before, during, and after treatment for PTSD with standardized dimensional measures of disease severity including the Clinician Administered PTSD Scale (CAPS), the Hamilton Rating Scale for Depression (HAM-D), and the Hamilton Rating Scale for Anxiety (HAM-A). Data were collected from November 2001 through June 2003.

Results: Phenytoin treatment resulted in a significant decrease in PTSD symptoms as measured with the CAPS (mean score = 65 pretreatment vs. 38 posttreatment) with reductions in each of the symptom clusters of intrusions, avoidance, and hyperarousal ($p < .05$). There were no significant decreases in symptoms of depression severity as measured with the HAM-D or anxiety severity as measured with the HAM-A.

Conclusions: These findings suggest that phenytoin may be efficacious in the treatment of PTSD, possibly mediated through its antiglutamatergic effects. Randomized, controlled, double-blind clinical trials are indicated to further evaluate this medication in the treatment of PTSD.

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Posttraumatic stress disorder (PTSD) is a disabling disorder that affects 8% of Americans at some time in their lives.[1] Developing and evaluating effective treatments for PTSD are critical for this disorder. Symptoms of PTSD can become chronic in many patients and, therefore, difficult to treat. Although some medications such as selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective for PTSD, not all patients will have a complete resolution of symptoms with currently available medications.[2]

Several studies have shown that antidepressant medications are efficacious in PTSD.[3–5] Controlled studies have shown that tricyclic medications including imipramine[6,7] and amitriptyline[8] are useful in the treatment of PTSD. Nightmares in PTSD patients were successfully treated with the α_1-noradrenergic antagonists prazosin[9] and guanfacine.[10] Medications acting on the μ opiate receptor (naltrexone)[11] and γ-aminobutyric acid (GABA) (pentagastrin)[12] systems have also shown some promise; studies of benzodiazepines (alprazolam)[13,14] have not. Serotonergic agents have provided much more promising results. The serotonin-2 ($5\text{-}HT_2$) receptor antagonist cyproheptadine was efficacious in some open-label studies but not others in PTSD patients.[15–18] SSRIs that were useful for PTSD in open-label trials include fluvoxamine[19] and paroxetine.[20,21] Large placebo-controlled trials revealed efficacy for the SSRIs sertraline[22] and paroxetine,[23] while mixed results have been obtained for fluoxetine.[24–28] Open-label studies involving agents with mixed actions

on serotonin receptors that showed positive efficacy include mirtazapine,[29] bupropion,[30] and nefazodone.[31–33] Some controlled studies were encouraging for nefazodone in veterans.[34] Several open-label studies in PTSD have shown efficacy for the atypical neuroleptic risperidone, which has actions on dopaminergic receptors, especially for symptoms of trauma-related hallucinations, flashbacks, aggression, and irritability.[35–38] Preliminary evidence also supports efficacy for the atypical antipsychotics olanzapine[39] and lamotrigine.[40] The findings from these studies have led to U.S. Food and Drug Administration approval for sertraline and paroxetine in the treatment of PTSD and to the recommendation that SSRIs be used as first-line agents in the treatment of PTSD.[41–44]

Cases of no response or only partial response with these medications, especially in patients with complex PTSD that is comorbid with other conditions, have led to the search for medications with alternative mechanisms of action to those of the SSRIs. The idea that the pathophysiology of PTSD may involve a kindling-like phenomenon within the hippocampus, analogous to the model used for epilepsy, has provided theoretical support for the use of anticonvulsants in PTSD. Open-label trials suggested efficacy for topiramate,[45] valproate,[45–47] and carbamazepine[47,48] Some of these medications have actions on glutamatergic systems, which are involved in the stress response[49] and are increasingly appreciated as playing a role in trauma-related symptoms.[50] Symptoms of dissociation, including out-of-body feelings or seeing things as if in a dream, are an important aspect of the trauma response and predict negative long-term outcome.[51,52] Administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine, which blocks glutamatergic function, leads to marked symptoms of dissociation in human subjects.[53] NMDA receptors are highly concentrated in the hippocampus, where they play a critical role in memory and long-term potentiation (LTP: a molecular mechanism for memory). Stress inhibits LTP.[54] Stress in animals also results in damage to hippocampal neurons with associated deficits in memory,[55,56] mediated at least in part through stress-induced increases in cortisol leading to decreased glucose utilization with associated glutamate toxicity in the hippocampus.[57,58] Patients with PTSD were found to have smaller hippocampal volumes or other hippocampal abnormalities as measured with magnetic resonance imaging[59–67] and to have deficits in hippocampal-based verbal declarative memory function.[68–81] A breakdown in memory is a central component of trauma-related dissociation, and 2 studies have correlated atrophy of the hippocampus (which is stress sensitive and plays a key role in memory) with dissociation symptom level in PTSD patients.[61,67]

Phenytoin, an anticonvulsant used in the treatment of epilepsy, blocks cellular responses to glutamate.[82,83] Moreover, calcium-mediated cellular functions (protein phosphorylation, neurotransmitter release) and calcium dependent depolarization, both associated with neuronal death, have been shown to be arrested by phenytoin.[84,85] In vivo, phenytoin decreased the dimension of cerebral infarct in animals with bilateral or unilateral carotid occlusion.[86,87] In animal studies, phenytoin was shown to prevent stress and corticosterone-induced atrophy of CA3 pyramidal neurons[88] and to reverse stress-induced impairment of spatial learning and hippocampal atrophy.[89] On the basis of these studies, we hypothesized that phenytoin would be efficacious in the treatment of PTSD.

SUBJECTS AND METHOD

Twenty-eight subjects were initially screened for participation in this study. Fourteen subjects were excluded because they did not meet criteria for PTSD or they were taking a benzodiazepine or neuroleptic. Fourteen subjects signed a consent form, and 2 dropped out before they initiated treatment. Twelve subjects started treatment, and 3 did not complete treatment (described below). Nine male (N = 4) and female (N = 5) subjects who were 18 years of age or older and met criteria for PTSD completed participation in the study. All subjects were recruited by advertisement and gave written informed consent for participation in the study. This study was approved by the Emory University Investigational Review Board.

PTSD subjects were included with the diagnosis of PTSD based on the Structured Clinical Interview for DSM-IV (SCID).[90] PTSD patients had experienced a range of traumas including childhood abuse (N = 4), domestic violence (N = 2), motor vehicle accident (N = 1), assault (N = 1), and combat (N = 1). Subjects were excluded if they presented with a history of current alcohol or substance abuse or dependence in the past 6 months, schizophrenia, or an eating disorder as determined by the SCID; serious medical disorder as determined by laboratory tests and physical examination; organic mental disorder; neurologic disorder; or head trauma. Subjects were excluded who were treated with benzodiazepines or neuroleptics for 6 months before the study.

Subjects did not discontinue medication for the purpose of participation in this study. No subjects in this study were taking a psychotropic or were in psychotherapy at the time they entered into the study. They did not initiate psychotherapy or an alternative medication treatment during the course of the study. They were only seen for follow-up medication treatment during the course of the study. Data were collected from November 2001 through June 2003.

All subjects were evaluated with the SCID for comorbid psychiatric diagnoses. Six of 9 PTSD subjects (67%) fulfilled criteria for a lifetime history of major depressive disorder and none for a current major depressive episode. One subject (11%) fulfilled criteria for lifetime and cur-

Table 1. Effect of Open-Label Phenytoin on PTSD Symptom Clusters[a]

CAPS Symptom Score	Baseline	4 Weeks	8 Weeks	12 Weeks
Intrusions	18 (6)	11 (8)	9 (8)	9 (9)
Avoidance	25 (16)	20 (14)	17 (12)	15 (10)
Hyperarousal	22 (6)	15 (6)	13 (7)	13 (7)
Total	65 (22)	46 (21)	39 (20)	38 (24)

[a]All values are mean (SD).
Abbreviations: CAPS = Clinician Administered PTSD Scale, PTSD = posttraumatic stress disorder.

Table 2. Effect of 12 Weeks of Open-Label Phenytoin on Individual PTSD Symptoms According to Change in CAPS Item Score (range 0–8)

Symptom	Change
Intrusive memories	–1.20
Nightmares	–1.70
Reexperiencing	–1.20
Feeling upset with reminders	–2.44
Increased physiologic arousal with reminders	–2.33
Avoidance of thinking about trauma	0.00
Avoidance of reminders of the trauma	–2.89
Amnesia for aspects of the event	–1.33
Decreased interest in things	–0.22
Feeling cut off from others	–1.56
Emotional numbing	–0.22
Sense of foreshortened future	–2.00
Insomnia	–2.33
Irritability	–0.33
Decreased concentration	–1.67
Hypervigilance	–1.00
Increased startle	–1.56

Abbreviations: CAPS = Clinician Administered PTSD Scale, PTSD = posttraumatic stress disorder.

rent history of panic disorder without agoraphobia and social phobia. None of the subjects had lifetime or current alcohol or substance abuse/dependence.

All PTSD subjects were assessed with the Clinician Administered PTSD Scale (CAPS),[91] a reliable and valid measure of PTSD symptom severity with subcomponents for the individual symptom clusters. Current depressive symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D).[92] State anxiety was measured with the Hamilton Rating Scale for Anxiety (HAM-A).[93]

Subjects were treated with a variable dose of phenytoin in an open-label fashion for 3 months. Treatment was started at 300 mg/day divided into 3 doses and increased to 400 mg/day if blood levels were subtherapeutic. Blood levels of phenytoin were obtained at weeks 1, 2, 3, 4, 8, and 12, and dose was adjusted to be within the therapeutic range used in the treatment of epilepsy (10–20 ng/mL). Subjects were treated with folic acid to prevent folic acid deficiency due to phenytoin. Twelve patients started the study, 2 patients dropped out because of side effects, and 1 patient was relocated out of state. Behavioral ratings of PTSD, depression, and anxiety were obtained at baseline and every 4 weeks.

Paired t test was used to assess the effects of phenytoin on PTSD and other symptoms. Significance was defined as $p < .05$.

RESULTS

Phenytoin administration resulted in a significant decrease in PTSD symptoms (Table 1). There was a 27-point drop in the mean CAPS score with 12 weeks of treatment ($t = –3.82$, $df = 7$, $p = .005$). Reductions were seen in each of the symptom clusters of intrusions, avoidance, and hyperarousal ($p < .05$). Symptoms started to improve within the first 4 weeks and continued to improve until the end of the study. Some of the symptoms that showed the greatest change were reexperiencing, avoidance of reminders, physiologic responses to reminders, feeling upset with reminders, sense of foreshortened future, and insomnia (Table 2; $p < .05$). There were also improvements from baseline to week 12 in mean (SD) scores on several CAPS-based measures (rated from 0 = not at all to 4 = extreme) including subjective distress (2.7 [SD = 0.7] to 1.7 [SD = 0.7]), social function (2.6 [SD = 1.3] to 1.3 [SD = 1.4]), occupational function (1.8 [SD = 1.2] to 1.2 [SD = 1.4]), and global severity (2.1 [SD = 1] to 1.4 [SD = 1.4]). There was no effect on symptom severity of depression or anxiety as measured by the HAM-D or HAM-A, respectively. There were no significant differences in symptom response as measured with the CAPS between childhood trauma versus adult trauma patients (mean change in CAPS score with treatment = –38 [SD = 21]) vs. –19 [SD = 20]).

COMMENT

The data from this study were consistent with efficacy for phenytoin in the treatment of PTSD. Symptoms began to improve within the first 4 weeks and continued to gradually improve until the end of the study. Phenytoin was also associated with improvements in social and occupational function as well as subjective distress. There was no effect of phenytoin on symptoms of anxiety or depression.

One possible mechanism of action of phenytoin in the treatment of PTSD is its effect on glutamatergic function. Phenytoin has been shown in laboratory animal studies to antagonize glutamate-induced excitation of cerebrocortical neurons[94] and to block the effect of glutamate at the NMDA receptor.[82,83] Phenytoin differs from other antiepileptic medications such as carbamazepine in its mechanism of action related to the glutamatergic system.[83] The chronic stress of PTSD could be associated with ongoing glutamatergic toxicity that is benefited by phenytoin treatment. Kindling phenomena have been hypothesized to underlie the pathophysiologies of both epilepsy and mood and anxiety disorders. In kindling, repeated stimulation in

the hippocampus or amygdala leads to an enhancement of the postsynaptic potential and an increased risk of seizures. Phenytoin results in a decrease in seizures in kindled animals.[95]

Some studies have provided evidence for the efficacy of phenytoin in the treatment of anxiety disorders and depression. Phenytoin blocked the anxiety induced by the benzodiazepine receptor antagonist Ro 5-4864 in healthy human subjects.[96] Other studies showed efficacy in the treatment of anxiety,[97,98] hostility,[99–101] and depression.[102] These studies, however, used diagnostic categories that are no longer in use and had other limitations to their applicability to current practice. Controlled trials of phenytoin in the treatment of psychiatric disorders in the past 2 decades have been virtually nonexistent.

The current study has several limitations. Most prominent among them are the open-label nature of the study and the small sample size. Prior studies have shown as much as a 23-point drop in CAPS score with placebo[23]; therefore, we can't rule out that the results are a placebo effect. Future studies using a double-blind, randomized, placebo-controlled design should be performed.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), fluoxetine (Prozac and others), guanfacine (Tenex and others), imipramine (Tofranil, Surmontil, and others), ketamine (Ketalar and others), lamotrigine (Lamictal), mirtazapine (Remeron and others), naltrexone (Revia and others), nefazodone (Serzone and others), olanzapine (Zyprexa), paroxetine (Paxil and others), phenytoin (Dilantin and others), prazosin (Minipress and others), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax).

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