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An Open-Label Pilot Study of Divalproex Sodium for Posttraumatic Stress Disorder Related to Childhood Abuse

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ABSTRACT

Background: Few effective pharmacotherapeutic strategies have been established for the treatment of symptoms associated with posttraumatic stress disorder (PTSD). Preliminary evidence supports the efficacy of serotonergic agents and anticonvulsants, such as divalproex sodium, for the treatment of PTSD symptoms, particularly in military populations.

Objective: The aim of this study was to obtain pilot data on the use of divalproex sodium for the treatment of PTSD among adult civilian outpatients with a history of childhood physical and/or sexual abuse.

Methods: Outpatients with a primary psychiatric diagnosis of PTSD received open-label, flexibly dosed divalproex sodium as adjuvant therapy or monotherapy for 8 weeks. Overall and subcluster PTSD features, as well as affective symptoms and clinical global improvement, were monitored using standardized assessment scales.

Results: A total of 7 patients (5 women, 2 men; mean age, 44.1 years [range, 29–57 years]) were enrolled. At a mean (SD) peak dosage of 1500 (661) mg/d, significant improvement occurred in overall PTSD symptom severity ($P < 0.02$) and in the diagnostic subclusters of hyperarousal and avoidance ($P < 0.02$ for both). Depressive symptoms also were significantly improved from baseline ($P < 0.02$). Divalproex sodium was well tolerated, except in 1 patient who prematurely discontinued treatment due to cognitive adverse events.

Conclusions: These provisional findings support the possible utility of divalproex sodium therapy for adult outpatients with PTSD related to physical and/or sexual abuse during childhood. Controlled trials with larger sample sizes powered to show safety and efficacy are needed to substantiate these initial

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Key words: posttraumatic stress disorder, divalproex sodium, trauma, anticonvulsant.

INTRODUCTION

Posttraumatic stress disorder (PTSD) has been reported to occur in 5% to 10% of the adult population, with a somewhat higher prevalence among women than men.[1] Optimal treatment may involve a combination of pharmacotherapy and psychotherapy.[2,3] However, studies of pharmacotherapy for PTSD typically have shown partial improvements in some, but not all, PTSD symptom clusters. At present, the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are the sole pharmacotherapies approved by the US Food and Drug Administration for the treatment of PTSD.[4–6] Other SSRIs, such as fluoxetine[7] and the novel serotonergic compound nefazodone,[8,9] have been reported in open trials to produce improvement in the 3 broad PTSD symptom clusters of reexperiencing, avoidance, and hyperarousal. Less robust efficacy has been reported with monoamine oxidase inhibitors, tricyclic antidepressants, and benzodiazepines.[10–13] Partial improvement and incomplete remission of particular symptoms, including anger and sleep disturbances, are common.[9] Moreover, comorbid psychopathology, especially symptoms of depression and anxiety, may be evident in up to 80% of patients with PTSD.[11,14]

Anticonvulsant mood stabilizers have received increasing attention as alternative remedies for PTSD-related symptoms. Notably, carbamazepine has been associated with improvement in flashbacks, nightmares, and reexperiencing (ie, intrusive thoughts),[15–17] and divalproex sodium has been reported to improve reexperiencing, hyperarousal/hyperreactivity, avoidance, and anger/aggression.[17–20] Data from open trials suggest a role for other anticonvulsants, such as lamotrigine[21] or topiramate.[22] Because most reports have focused on combat-related PTSD in male military veterans, the generalizability of the findings to PTSD in civilian populations has not yet been studied extensively.

We report findings of an open-label pilot study of divalproex sodium in adult civilian outpatients with PTSD related to childhood physical and/or sexual abuse.

PATIENTS AND METHODS

The patient sample was drawn from the Anxiety and Traumatic Stress Program of the Payne Whitney Clinic, New York Presbyterian Hospital, New York, New York. The index trauma for the diagnosis of PTSD was childhood physical and/or sexual abuse, which provided homogeneity in the study sample. Participants were self-referred or referred by clinicians in the community for the nonemergent treatment of PTSD symptoms and were self-selected into this study.

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[23] *(DSM-IV)*–defined diagnosis of PTSD after childhood physical and/or sexual abuse was established by *Structured Clinical Interview for DSM-IV Axis I Disorders*[24] (*SCID-I/P*) interviews conducted by trained, experienced clinical interviewers. For the purposes of study inclusion, all patients were required to be at least 18 years of age, not actively psychotic or suicidal, nonpregnant and nonlactating (if a female of childbearing potential), have no unstable medical comorbidities, and able to provide informed consent to participate. In addition, for the 3 months prior to the initial assessment, all participants were required to have PTSD symptoms regardless of other treatments. These symptoms were not responsive to current concomitant treatments.

Screening assessments also included a medical history and physical examination, as well as biochemistry profile, complete blood count, urine toxicologic screening examination, and electrocardiography.

Patients who met *DSM-IV* criteria for psychiatric diagnoses in addition to PTSD (eg, major depression) were included if, by consensus judgment of the investigators, such diagnoses were either thought to be secondary to a primary diagnosis of PTSD or thought not to be significant contributors to current PTSD symptoms.

Patients taking other psychotropic drugs prior to study enrollment were allowed to continue with treatment at the established dosage during the study period.

All patients provided written informed consent to participate, and the research protocol was approved by the Committee on Human Rights of the Weill Medical College of Cornell University, Ithaca, New York.

Open-label treatment with divalproex sodium began at 250 mg twice daily and continued over an 8-week period; the dosage was increased by 250 mg/d every 3 to 7 days as needed to achieve a clinical response based on PTSD symptom ratings and medication tolerability. Liver function tests were performed before treatment and at study conclusion. Serum trough valproic acid levels were measured ~10 to 14 hours after a previous dose, at week 1 and again at study conclusion. Patients were seen weekly throughout the study for clinical assessments and monitoring of treatment response and adverse events.

PTSD symptoms were assessed before and after treatment using the Posttraumatic Stress Disorder Symptoms Scale–Self Report[25] (PSS-SR) as the primary outcome measure. This widely used 17-item instrument measures the frequency and severity of symptoms for the PTSD subclusters of reexperiencing, hyperarousal, and avoidance, and gives a total summed assessment of the 17 PTSD symptoms. Secondary outcome measures included ratings of symptoms of depression (using the 31-item Hamilton Rating Scale for Depression[26] [HAM-D] and the Beck Depression Inventory[27] [BDI]), and symptoms of anxiety (using the 14-item Hamilton Rating Scale for Anxiety[28] [HAM-A]). Clinical improvement was defined as a ≥33% reduction from baseline PSS-SR ratings. Anger and hostility were assessed with the State-Trait Anger Expression

Inventory[29] (STAXI) and the hostility subscale of the Brief Symptom Inventory[30] (BSI).

Pretreatment and posttreatment changes in mean frequency and severity of symptoms were analyzed using the Mann-Whitney *U* test. A within-group effect size was calculated to assess the magnitude of change over time in PTSD symptoms.[31] Statistical significance was set at $P < 0.05$.

RESULTS

The study comprised 7 patients (5 women, 2 men; mean age, 44.1 years [range, 29–57 years]). Six patients were receiving psychotherapy at the time of study entry. Treatment and clinical characteristics of the study patients are presented in Table I. Patients received a mean (SD) peak divalproex sodium dosage of 1500 (661) mg/d and achieved a mean (SD) peak serum valproic acid level of 90.3 (59.4) μg/mL.

The most commonly encountered adverse events were gastrointestinal upset (4 patients), sedation (2), weight gain (1), and tremor (1). One patient with comorbid osteoarthritis who took methadone for pain prematurely discontinued the trial at week 2 due to cognitive adverse events, which resolved completely when divalproex sodium was discontinued.

Table II shows each patient's PSS-SR severity scores at baseline and weeks 2, 4, 6, and 8 of treatment, as well as the group mean (SD) of the PSS-SR scores. A significant difference from baseline to study end was observed in mean PSS-SR total scores ($P < 0.02$), as well as a substantial within-group effect size of 1.70. Significant improvements also were found in PSS-SR subscales for hyperarousal (25.4 [13.6] pretreatment, 15.7 [11.6] posttreatment; $P < 0.02$) and avoidance (27.1 [14.4] pretreatment, 15.7 [12.1] posttreatment; $P < 0.02$). A trend toward reduction in the PSS-SR reexperiencing subscale was found (25.4 [13.6] pretreatment, 15.7 [11.6] posttreatment).

A clinical response was achieved and sustained in PSS-SR total scores for 4 of the 7 patients (57.1%). PSS-SR subcomponent measures were associated with improvement of ≥33% from baseline in hyperarousal and avoidance in 4 patients (57.1%) each and in reexperiencing in 5 patients (71.4%).

Significant improvement in depression ratings was observed based on mean (SD) BDI scores (29.4 [12.9] pretreatment, 22.9 [13.4] posttreatment; $P < 0.02$). A trend toward improvement in symptoms of depression as measured by HAM-D ratings was noted from pretreatment (30.6 [20.6]) to posttreatment (19.0 [11.3]). A decline in HAM-A anxiety scores was nonsignificant from pretreatment (20.4 [17.4]) to posttreatment (13.6 [8.4]). No changes were seen in anger expression (35.2 [5.8] pretreatment, 32.3 [11.2] posttreatment). However, a significant reduction was observed in the BSI-hostility index, which reflects the severity and frequency of annoyance, irritability, and outbursts of temper (1.87 [0.86] pretreatment, 1.16 [1.14] posttreatment; $P < 0.05$).

Table I. Treatment and clinical characteristics of patients with posttraumatic stress disorder.

Patient No.	Age, y	Race	Sex	Peak Divalproex Sodium Dosage, mg/d	Peak Serum Valproic Acid Concentration, μg/mL	Comorbid Diagnoses	Concomitant Psychotropic Medications
1	45	W	M	2500	46.8	HIV ($CD4^+$ = 625 cells/mm^3)	Amitriptyline 25 mg/d
2	53	W	M	1000	N/A	None	None
3	51	W	F	1250	120.0	Unipolar depression	Sertraline 75 mg/d
4	38	H	F	1500	66.7	Unipolar depression	Sertraline 50 mg/d, trazodone 50 mg/d, cimetidine 20 mg/d
5	36	W	F	1750	37.8	Unipolar depression	Bupropion 400 mg/d, clonazepam 4 mg/d
6*	57	B	F	500	N/A	Residual schizophrenia, osteoarthritis/chronic pain	Perphenazine 20 mg/d, benztropine 4 mg/d, diazepam 15 mg/d, nortriptyline 25 mg/d, methadone 30 mg/d
7	29	H	F	2000	180.0	Unipolar depression, borderline personality disorder	Sertraline 200 mg/d

W = white; M = male; HIV = human immunodeficiency virus; N/A = not available; F = female; H = Hispanic; B = black.
*Discontinued treatment.

Table II. Changes in Posttraumatic Stress Disorder Symptoms Scale–Self Report[25] scores.

	Score				
Patient No.	Baseline	Week 2	Week 4	Week 6	Week 8
1*	60	ID	ID	ID	11
2	59	56	72	38	46
3*	102	60	45	99	59
4*	97	98	94	62	63
5	95	104	70	55	65
6	40	27	35	ID	35
7*	16	15	ID	2	0
Mean (SD) score	67 (33)	60 (36)	63 (23)	51 (35)	40 (35)†

ID = incomplete data at assessment.
*Patient achieved and sustained a clinical response.
†$P < 0.02$ (Mann-Whitney U test).

DISCUSSION

Divalproex sodium was well tolerated in all but 1 patient in this study, and the majority of patients showed signs of response, typically within 4 to 5 weeks of initiating treatment. Our observed rate of premature study discontinuation due to adverse events (14%) was comparable to that reported by Pope et al[32] for the treatment of acute mania (12%), although somewhat higher than that observed by Bowden et al[33] in a large group of patients with acute mania (6%). Significant improvement was observed in overall PTSD features, in 2 of the 3 component dimensions of PTSD, and in symptoms of depression present before treatment compared with after treatment. Reduction in PTSD symptoms may be the result of the hypothesized antikindling activity associated with divalproex sodium,[34] an explanation derived from the observed success of this medication in the treatment of bipolar affective disorder[32,33] and panic disorder.[32,35–37] The improvement in depressive symptoms is consistent with the results of the largest study of divalproex sodium for major depression (an open-label study of 32 patients[38]) and an open-label study of 16 male combat veterans with PTSD.[18]

Whether a therapeutic window for serum valproic acid levels in the treatment of PTSD exists, as exists for bipolar disorder, is unknown.[39] Previous open-label trials in PTSD using divalproex sodium or other mood stabilizers, such as lithium, have not described parameters for drug efficacy relative to serum levels. A dose-response or serum level–response relationship was not evident based on the small number of patients for whom serum valproic acid levels were available in this study. Larger studies are needed to address this issue.

Of particular interest were the potential ameliorative effects of divalproex sodium on hostility, as measured in this study using the BSI-hostility index. Anger has been identified as a strong predictor of poor outcome in the psychotherapy of rape victims[40] and combat veterans with PTSD.[41] No changes in pretreatment

compared with posttreatment values on the STAXI were found; however, significant reductions in BSI-hostility were shown. The latter measure may be more sensitive to the presence of anger than the STAXI, which assesses skill in managing anger. These results suggest that divalproex sodium may be a useful adjunctive pharmacologic agent for managing patients with anger associated with PTSD who receive psychotherapy. These preliminary findings support those of other studies[17–20] that have demonstrated improvement in PTSD symptoms during open-label treatment with divalproex sodium across diverse populations of PTSD patients.

It is possible that the structure of the current study protocol, including systematic visits and symptom assessment, may in itself have enhanced a placebo-like effect that may have influenced response status. However, because all patients had been receiving treatment prior to study entry, this seems unlikely.

Limitations of the current pilot study include the small sample size; the open-label design; the presence of comorbid secondary psychiatric diagnoses; and the use of concomitant, preexisting psychotropic medications by some patients. The open-label, nonrandomized design did not permit assessment of possible temporal or placebo effects leading to improvement. Because divalproex sodium inhibits cytochrome P-450 microenzymes, it is theoretically possible that its augmentation of some antidepressants (or other drugs metabolized by this system) may have led to pharmacokinetic or pharmacodynamic changes associated with clinical improvement. Most patients with PTSD have been shown to have additional comorbid psychiatric disorders related to affective illness and/or other anxiety syndromes.[1] In this respect, the current study population was representative of typical community-based adults with PTSD. The presence of PTSD symptoms at study entry in patients with comorbid psychopathology, despite prior pharmacotherapy (including SSRIs or other antidepressants) and psychotherapy, underscores the often treatment-resistant nature of PTSD symptoms and the frequent need for multimodal interventions. Similarly, the magnitude of symptom improvement from baseline levels of PTSD severity was not suggestive of full remissions in the current study group, although a substantial within-group effect size was observed in the primary PTSD outcome measure. Partial rather than full remission of PTSD symptoms has been observed in a prior study[42] of both pharmacotherapy and psychotherapy in patients with PTSD.

CONCLUSIONS

These provisional findings support the possible utility of divalproex sodium therapy for adult outpatients with PTSD related to physical and/or sexual abuse during childhood. Controlled trials with larger sample sizes powered to show safety and efficacy are needed to substantiate these initial findings.

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