Divalproex Sodium for Impulsive Aggressive Behavior in Patients With Personality Disorder

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Objective: Divalproex sodium, an anticonvulsant and antimanic agent, has recently been studied for its antiaggressive effects in patients with brain injuries, dementia, and borderline personality disorder. Since patients with other personality disorders also exhibit impulsive aggressive behavior, we conducted a preliminary open-label trial of divalproex sodium as a treatment for irritability and aggression in patients with a variety of personality disorders.

Method: Ten patients meeting DSM-IV criteria for at least one personality disorder were treated with divalproex sodium in an 8-week open clinical trial. All patients had failed a trial of a selective serotonin reuptake inhibitor (SSRI). Divalproex sodium was increased as tolerated using a flexible dosing schedule. Clinician ratings for impulsive aggressive behavior and irritability were made every 2 weeks using the modified Overt Aggression Scale (OAS-M).

Results: Six of 8 completers reported significant decreases in irritability ($p = .003$) and impulsive aggressive behavior ($p = .019$). For the entire sample, improvement on OAS-M irritability and overt aggression scores was noted by the end of 4 weeks and continued to occur through week 8.

Conclusion: This study suggests that divalproex sodium is an effective treatment for impulsive aggressive behavior in some patients with personality disorder who fail to respond to other antiaggressive agents (i.e., SSRIs). Controlled studies are needed to determine which patients are most likely to benefit from divalproex sodium and to evaluate the differential effectiveness of various agents in reducing impulsive aggressive behavior.

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The appropriate use of medications in patients with personality disorders remains equivocal. Many agents have been suggested as beneficial (e.g., neuroleptics, selective serotonin reuptake inhibitors [SSRIs], lithium), but there is little guidance for the clinician in making a decision about which medication to use for a particular patient. Problems with accurate diagnosis, overlap between personality disorders, and poor compliance have made it difficult to conduct and interpret studies of pharmacologic treatment of these patients. In addition, current thinking suggests that rather than treating any one particular personality disorder, medications appear to treat individual pathologic personality traits[1] (e.g., neuroleptics for brief psychotic episodes, mood stabilizers for affective lability).

Abnormalities in the brain's serotonin systems may predispose individuals to aggressive behavior. For example, the major metabolite of serotonin, 5-hydroxyindoleacetic acid, is reduced in the cerebrospinal fluid of subjects with a history of aggression (violence toward others and violent suicide attempts) compared with those with no such history.[2] Neuroendocrine studies also show evidence of a relationship between decreased central serotonin function and impulsive aggression. There is a strong inverse relationship between the prolactin response to fenfluramine challenge (a putative measure of central serotonin functioning) and measures of irritable, impulsive aggression in male patients with personality disorder whatever the particular personality disorder.[2] These findings suggest that medications which increase central serotonin function should be helpful in patients with such problems. In fact, SSRIs have been found to be effective in reducing impulsive aggressive behaviors in patients with a variety of personality disorders.[3,4] However, a substantial number of patients do not seem to benefit from these medications. In a placebo-controlled, double-blind study, 27% of patients did not respond to treatment with fluoxetine.[4] Thus, it is important to have alternative options for medication management of these behaviors.

Medications used to treat mania reduce affective lability and thus may decrease behavioral lability and aggression as well. Lithium has been long recognized as having antiaggressive effects. Lithium has been reported to reduce impulsive aggression in prison inmates in both open[5] and blinded placebo-controlled trials.[6] Lithium was more

effective than placebo in reducing mood lability in a group of adolescent girls with "emotionally unstable character disorder," a group of patients characterized by intense, rapidly shifting affects and impulse control problems.[7] In a double-blind, placebo-controlled, randomized crossover study in patients with borderline personality disorder, lithium was superior to desipramine in reducing anger and suicidal and impulsive symptoms of borderline patients.[8] Another double-blind, placebo-controlled, crossover trial comparing alprazolam, tranylcypromine, trifluoperazine, and carbamazepine found the antimanic agent carbamazepine to be the only medication that decreased behavioral outbursts in patients with borderline personality disorder.[9] Preliminary reports suggest that divalproex sodium is also effective in reducing aggression in a variety of patient populations, including individuals with traumatic brain injury,[10] adolescents with chronic temper outbursts and mood lability,[11] and patients with borderline personality disorder.[12,13] However, the efficacy of this agent has not been studied in patients with other personality disorders.

To test the efficacy of divalproex sodium in the treatment of impulsive aggressive behavior, we conducted an open-label pilot trial of this medicine in impulsive aggressive DSM-IV patients with personality disorder who had failed a trial of the SSRI fluoxetine.

METHOD

The patients discussed in this report were enrolled in a specialized assessment program for personality disorders. Patients met DSM-IV criteria for at least one Axis II personality disorder as determined by the Structured Interview for DSM-IV Personality Disorders (SIDP-IV).[14] Patients were excluded if they met Axis I criteria for schizophrenia, bipolar disorder (I or II), alcohol or drug dependence, or organic mental syndrome based on the Structured Clinical Interview for DSM-IV.[15] All patients were without significant medical problems. Patients had been treated with fluoxetine, an SSRI, at least 60 mg/day for at least 8 weeks. All patients had been off treatment with fluoxetine and other psychotropic medications for at least 2 weeks. Patients gave written informed consent to participate in the study.

To measure impulsive aggression, we used the modified Overt Aggression Scale (OAS-M). This is a clinician-administered assessment that measures overt irritability and assault (both verbal and physical) over a specified interval, usually the past week.[16] It is a modified version of the Overt Aggression Scale developed by Yudofsky et al.[17] to assess objective verbal and physical aggression among inpatients. The OAS-M grades different types of aggression according to weighted scores. Scores are given for both overt aggression and irritability. Interrater reliability is high (intraclass correlation = 0.93). To be treated in this open trial of divalproex sodium, patients had to have a minimal baseline OAS-M aggression score > 15 and a minimum OAS-M irritability score > 6, suggesting clinically significant impulsive aggression and the conditions for entry into our double-blind study of fluoxetine versus placebo.[4]

All patients were treated as outpatients. Patients were started on treatment with divalproex sodium, 500 mg each morning. The dose was increased as tolerated until the patient was responding clinically, to a maximum of 2000 mg each morning. Repeat OAS-M scores were obtained at 2, 4, and 8 weeks on the medication therapy. Changes from baseline in mean OAS-M scores at weeks 2, 4, and 8 were analyzed using paired Student t tests (2-tailed). Improvement was defined as a greater than 50% decrease in OAS-M aggression and irritability at the end of the trial compared with baseline.

RESULTS

Ten patients entered the trial. Demographics, diagnoses, weeks of treatment, and maximum dose taken are listed in Table 1. One patient stopped treatment after 4 weeks, and another stopped after 6 weeks (not compliant with medical monitoring of medication).

For the 10 patients who took medication for at least 4 weeks, improvement was noted on both measures of overt aggression and irritability (Table 2). Mean OAS-M aggression scores showed improvement beginning at week 2 ($t = 2.50$, $df = 9$, $p = .034$) and continuing at week 4 ($t = 2.89$, $df = 9$, $p = .018$), week 6 ($t = 3.30$, $df = 8$, $p = .011$), and week 8 ($t = 3.03$, $df = 7$, $p = .019$). Mean OAS-M irritability scores were not significantly lower than baseline until week 4 ($t = 4.07$, $df = 9$, $p = .003$), week 6 ($t = 3.75$, $df = 8$, $p = .006$), and week 8 ($t = 4.46$, $df = 7$, $p = .003$). Of the 8 completers, 6 had a 50% or greater reduction of aggression and irritability on the OAS-M and were rated as significantly improved over baseline.

Three cases are reported in detail to illustrate the presentation of these patients and their response to treatment.

Case Reports

Patient 1. Ms. A, a 25-year-old single woman, presented for treatment at the insistence of her family. She reported a long history of temper outbursts and would frequently throw objects at others or break things (e.g., dishes) during heated arguments. She reported that these temper outbursts occurred several times per week, sometimes with minimal provocation. Her boyfriend was threatening to break up with her if she did not seek treatment. She had lost her most recent job because of her temper and complained of rapidly shifting moods. However, she denied any discrete episodes of hypomania, mania, or depression. Previous treatment with fluoxetine, up to 80

Table 1. Patient Demographics for Divalproex Sodium Treatment of Impulsive Aggression

Patient	Age	Sex	Axis I Diagnosis	Axis II Diagnosis	Weeks Completed	Maximum Dose (mg/d)
1	26	M	None	Schizotypal personality disorder, borderline personality disorder	4	1000
2	25	M	None	Borderline personality disorder	8	1500
3	26	M	None	Antisocial personality disorder, borderline personality disorder	8	1000
4	54	M	Obsessive-compulsive disorder	Avoidant personality disorder, obsessive-compulsive personality disorder	8	1000
5	32	F	Major depressive disorder	Avoidant personality disorder, obsessive-compulsive personality disorder	6	1500
6	38	M	Major depressive disorder	Paranoid personality disorder, obsessive-compulsive personality disorder	8	2000
7	25	F	None	Histrionic personality disorder	8	2000
8	48	M	None	Antisocial personality disorder, narcissistic personality disorder	8	1500
9	44	M	Major depressive disorder	Borderline personality disorder	8	2000
10	26	M	None	Paranoid personality disorder, borderline personality disorder	8	2000

Table 2. Divalproex Treatment of Impulsive Aggression: OAS-M Scores by Patient[a]

	OAS-M Aggression Scores					OAS-M Irritability Scores				
Patient	Baseline	Week 2	Week 4	Week 6	Week 8	Baseline	Week 2	Week 4	Week 6	Week 8
1	31	28	30	...	...	7	7	6	...	...
2	20	18	0	0	4	7	6	0	0	1
3	18	19	4	2	2	6	6	2	2	0
4	15	7	3	0	0	6	5	1	0	0
5	17	10	15	12	...	6	6	6	6	...
6	42	44	7	0	0	8	8	2	0	0
7	15	12	10	12	13	6	6	5	6	6
8	16	10	0	0	0	6	5	0	0	0
9	23	25	20	19	20	6	6	6	6	6
10	75	70	15	20	15	8	8	2	3	2
Mean	27.2	24.3	10.4	7.2	6.8	6.6	6.3	3.0	2.6	1.9
SD	17.9	18.5	9.2	8.0	7.5	0.8	1.0	2.4	2.6	2.5

[a]Abbreviation: OAS-M = Modified Overt Aggression Scale. Symbol: ... = medication was discontinued before this time point.

mg/day for 3 months, and supportive psychotherapy had been unsuccessful. Ms. A was started on divalproex sodium, 500 mg b.i.d., and the dose was increased to 1000 mg b.i.d. after 2 weeks. After 4 weeks of treatment, Ms. A reported decreased temper outbursts, verbal aggression, and irritability. This change was also noted by her family and boyfriend.

Patient 2. Mr. B, a 38-year-old married man, came to the clinic "because I'm out of control." He had a long history of temper problems dating back to adolescence and felt he was getting worse since being laid off from work. He felt that the company and their agents were trying to make it difficult for him to receive unemployment compensation, but he had no evidence of delusional thinking. He was losing his temper at least twice a week and had recently pushed a neighbor through a window in anger. He also had smashed his television during an argument with his wife. He decided to come in for treatment when his 5-year-old son said, "Daddy, I'm afraid of you." He began treatment with fluoxetine for 8 weeks, gradually increasing the dose during that time to 60 mg/day. He denied any change and requested another medication. After 2 weeks, divalproex sodium was begun at 1000 mg/day. He began to report less aggressive behavior once the dose was increased to 2000 mg/day at week 2. However, he attributed this to "willpower" and stopped the medication after 8 weeks. He returned to the clinic 1 month later, reporting a return of aggressive behavior and stating that "the medication helped me more than I thought."

Patient 3. Mr. C, a 54-year-old married man, was referred to the clinic by his wife, who complained that he had a volatile temper and would get angry at seemingly trivial frustrations. She reported that he would lose his temper several times per week, shouting and throwing objects in the living room. Although this had been his pattern throughout most of their marriage, his anger appeared to be intensifying and he had recently slapped her on 2 occasions. Mr. C had few friends outside of the home and did not usually lose his temper when at work. He was perfectionistic, and many of his outbursts occurred when his family did not "do things his way." He acknowledged his difficulties with his temper and seemed embarrassed by his behavior. Several weeks before coming to the clinic, he had seen his primary care physician, who had prescribed fluoxetine, 20 mg/day. His dose was gradually increased to 60 mg/day, but after a total of 8 weeks, neither he nor his wife noted much improvement. His medication was stopped, and 2 weeks later he began treatment with divalproex sodium. He was

started on 500 mg b.i.d., increasing to 1000 mg b.i.d. after 2 weeks. His wife reported a change in his behavior with fewer angry outbursts and decreased irritability. Although he noted little change, he was willing to remain on treatment with the medication "since my wife seems happy with it."

DISCUSSION

The results of this study support the hypothesis that antimanic agents such as divalproex sodium can be effective in reducing impulsive aggressive behavior in some patients with personality disorder. In this sample of patients who had failed a trial of an SSRI, open treatment with divalproex sodium decreased measures of overt aggression and irritability. Improvement was both statistically and clinically significant. The medication was generally well tolerated; no discontinuations were due to adverse events.

This study must be interpreted cautiously owing to the small number of subjects and the open nature of treatment. Although patients were off fluoxetine treatment for 2 weeks prior to starting treatment with divalproex sodium, it is possible that therapeutic levels of fluoxetine and/or norfluoxetine remained in the patients (owing to the long half-life of these agents), giving rise to therapeutic responses due to fluoxetine rather than divalproex sodium. However, in a double-blind trial of fluoxetine versus placebo in this population,[4] the number of responders to fluoxetine was maximized by week 8, suggesting that any delayed responses to fluoxetine after this point would be unlikely.

It is possible that the patients' responses were due to nondrug effects. It also might be argued that the impulsive aggression and irritability seen in these patients reflect an underlying affective disorder and that the effectiveness of the medication is due to treatment of the covert disorder. Patients were screened and excluded for bipolar disorders via structured instruments; however, there may be subclinical forms of cycling affective disorder that are difficult to diagnose.[18] Unfortunately, systematic assessments of depression, anxiety, and affective lability were not made in this open trial. The collection of such data in the future will help define to what extent divalproex sodium treatment specifically reduces impulsive aggressive behavior and may help predict those patients who will benefit from divalproex sodium as a first-line treatment for control of aggressive behavior.

Blood levels for divalproex sodium were not measured in our trial. Preliminary evidence suggests that acutely manic patients treated with divalproex sodium who have serum levels between 45 and 125 μg/mL have better responses than patients with lower or higher blood levels[19]; however, it still remains to be seen whether these levels will also be effective in the treatment of aggressive behavior. Future studies of divalproex sodium in the treatment of aggression should include blood levels to determine whether these would be helpful in guiding medication dosing in this population of patients.

Previous studies support the view that medications exert their effects on personality traits rather than on a particular personality disorder diagnosis. For example, Cowdry and Gardner[9] found that tranylcypromine was most effective in improving mood symptoms and impulsivity in borderline patients, whereas carbamazepine was most effective in the treatment of behavioral outbursts. In a double-blind trial, fluoxetine reduced impulsive aggression regardless of the specific personality disorder.[4]

This study adds to the literature on the pharmacologic treatment of personality disorders. Although other reports have described the beneficial effects of divalproex sodium in reducing aggressive behavior in certain populations, this is the first report of treatment nonresponders with a wide range of personality disorder diagnoses responding to this agent. This finding suggests that there are patients with impulsive aggression who respond better to antimanic agents than to serotonin medications. These results also suggest that different patients may have different biological vulnerabilities to this behavior. It is our task to attempt to determine which types of personality pathology respond preferentially to which pharmacologic agents in the treatment of aggression.

The exact mechanism of action of divalproex sodium in reducing impulsive aggressive behavior is unclear. As noted above, it may be that these patients have a subclinical affective disorder that is corrected by using antimanic agents. Personality disordered patients who engage in impulsive aggressive behavior often lack the verbal skills to adequately convey their dysphoria to their caretakers (e.g., family, therapist, hospital staff). Those individuals with subclinical bouts of affective symptoms may not be able to adequately describe their intensely shifting affects and thus are vulnerable to acting-out behavior. As in other areas of psychiatry, there is a dearth of knowledge regarding clinical predictors of response to medication. Future studies will need to determine a priori which patients would benefit most from treatment with SSRIs and which patients would benefit from antimanic agents such as divalproex sodium.

Drug names: alprazolam (Xanax), carbamazepine (Tegretol and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fenfluramine (Pondimin), fluoxetine (Prozac), tranylcypromine (Parnate), trifluoperazine (Stelazine).

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