Divalproex Sodium in Substance Abusers With Mood Disorder

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Background: Substance abuse is a common comorbid illness in patients with mood disorders. Little has been written about the pharmacologic treatment of patients with affective lability and co-occurring substance abuse, however. The following report will describe clinical experience using divalproex sodium in substance-abusing patients with mood disorder.

Method: Twenty patients admitted to an intermediate-care inpatient substance abuse program were diagnosed with comorbid mood disorder (according to DSM-IV criteria) and treated with divalproex sodium in an open-label, naturalistic trial with no blind. All patients were followed clinically and were assessed using the Clinical Global Impressions scale (CGI) and laboratory studies.

Results: Seven patients referred while on divalproex treatment continued to exhibit improved mood. Eleven others had at least 1 week of follow-up, and 10 of these also showed improvement. In 13 cases, divalproex was used safely with other psychiatric medications. Two patients complained of slight tremor, 1 of whom was also taking fluoxetine. Fifteen of 17 patients in whom biochemistry and hematology laboratory studies were completed had unremarkable results; 2 other patients had pretreatment abnormalities, which worsened over the course of treatment. Mean plasma valproate level was 58.53 μg/mL. Mean length of follow-up was 38 days. Mean period of abstinence prior to starting medication was 48 days. Some patients reported decreased cravings, and, by self-report, all patients remained abstinent.

Conclusion: This report suggests that divalproex sodium is efficacious and safe, both alone and in combination with other psychiatric medications, in treating substance-abusing patients with mood disorder.

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The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area study (ECA)[1] found a lifetime prevalence of bipolar disorder (I and II) of 1.3% in the United States. The lifetime prevalence of psychoactive substance use disorders (abuse and dependence) according to the same study was 16.7%. More recently, the National Comorbidity Survey (NCS)[2] demonstrated lifetime prevalence of mania to be 1.6% and that of substance use disorders to be 26.6%. Both the ECA and the NCS have shown that people with substance use disorders have higher rates of comorbid psychiatric illness than the population as a whole. These studies have also shown higher rates of substance use disorders in individuals with psychiatric disorders. Specifically, the ECA[1] found that 13.4% of alcoholics and 26.4% of nonalcohol drug abusers have an affective disorder. Conversely, that study showed that 56.1% of bipolar individuals abuse or are dependent on substances. Similarly, the NCS has demonstrated that 6.5% of alcoholic men and 10.6% of alcoholic women have a lifetime history of mania.[3]

The comorbidity of substance abuse and bipolar disorder adversely affects the course and outcome of both disorders.[4–13] For example, higher rates of mixed and rapid-cycling mania are found in bipolar patients with alcohol abuse disorder, and these patients take longer to recover.[4] As Brady and Sonne[14] have outlined, the higher rates of mixed, dysphoric, and rapid-cycling mania in substance abusers suggest the usefulness of divalproex sodium in these individuals, since data indicate that the anticonvulsants are more effective than lithium for these manic states.

Despite these data and the seriousness of the bipolar/substance abuse comorbidity as outlined above, little has been published on use of divalproex sodium in this population. In fact, as Brady et al.[15] note, studies of the phar-

macologic treatment of bipolar disorder usually exclude substance-abusing individuals. Brady et al.[15] used divalproex sodium in 9 acutely manic patients with comorbid substance use disorder. They found good resolution of affective symptoms, no adverse effects, and significant decrease in days of substance use during the follow-up period. This report will describe our clinical experience using divalproex sodium in substance-abusing patients with mood disorder, primarily bipolar type. It will address the medication's efficacy, safety, side effects, and use in conjunction with other psychiatric medications.

METHOD

Patients and Program

One hundred fourteen patients admitted to an inpatient substance abuse program were referred to one of the authors (M.J.A.) for psychiatric assessment. The program is a 170-bed voluntary inpatient unit for men who have completed detoxification. Patients receive individual counseling, as well as a full range of group treatments, including Alcoholics Anonymous. After a comprehensive clinical interview, DSM-IV substance use and non–substance use diagnoses were assigned to all men referred for psychiatric evaluation. Twenty patients were diagnosed with comorbid mood disorder and treated with divalproex sodium, including 7 who were referred while already taking the medication. All patients were white, with a mean age of 36 years (range, 20–55 years). Mean daily dose of divalproex was 1075 mg (range, 500–2000 mg).

Assessment

Patients were assessed by one clinician (M.J.A.), using the Clinical Global Impressions scale.[16] Emergence of side effects was also noted. Assessments occurred weekly while the patients remained in the program. Complete blood count (CBC), liver function tests, and plasma valproate level were also completed. Length of follow-up was calculated in all patients for whom a divalproex start date was known. Period of abstinence before evaluation was calculated in all patients for whom date of sobriety was known. At weekly assessment, patients were also asked about alcohol and drug use.

RESULTS

Patient characteristics, diagnoses, medications, and treatment outcomes are summarized in Table 1. The 7 patients who were referred while taking divalproex sodium continued to exhibit improvement in mood. Of the remaining 13 patients, 11 had at least 1 follow-up visit; 10 of these exhibited improved mood. One patient exhibited no change, but was lost to follow-up after a week. In 13 patients, divalproex sodium was combined safely with other psychiatric medications, mainly antidepressants. Two patients complained of slight tremor; 1 of these was also taking fluoxetine. No other side effects were reported.

In 17 patients, biochemistry and hematology laboratory studies were completed. Fifteen patients had unremarkable results. These included 2 patients with baseline liver function elevations that returned to normal levels over the course of treatment and 2 patients with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations at baseline that remained elevated but stable after divalproex was started. Of the remaining 2 patients, one exhibited elevated liver function levels prior to starting divalproex; the levels continued to rise after the medication was started and rose further despite stopping the medication. He was referred for hepatic evaluation and assessed for primary liver disease, but was lost to follow-up before a final diagnosis was made. We later learned he had been diagnosed with hepatitis C. Another patient had a low white blood cell count prior to starting divalproex and showed a further drop when the medication was added. The medication was discontinued, and the patient referred for hematology consultation; he was lost to follow-up.

Plasma valproate levels were obtained for 15 patients. Three patients left treatment before a level could be obtained; 2 refused to have a level measured. The mean plasma valproate level was 58.53 μg/mL.

In 12 patients, divalproex start date was known. Based on these cases, mean length of follow-up was 38 days (range, 7–108 days).

In half the patients, for whom date of sobriety was known, period of abstinence before evaluation was calculated. This period averaged 48 days (range, 14–108 days).

By self-report, all patients remained abstinent, and some patients reported decreased craving.

Case Reports

A sample of cases illustrating aspects of improvement that the patients experienced follows.

Patient 1. A 44-year-old married white man presented with diagnoses of bipolar disorder, type I, and alcohol dependence. The patient had been treated with divalproex in the past with resolution of his manic symptoms, but he had discontinued the medication and presented requesting that it be restarted. He initially appeared somewhat pressured and was started on treatment with divalproex sodium, 250 mg b.i.d. A week later, he reported feeling normal, and he remained this way through 4 weeks of follow-up. He experienced no side effects, and CBC and liver function test results remained within normal limits.

Patient 2. A 34-year-old single white man presented with alcohol dependence, cannabis abuse, and bipolar disorder, type II. He had been started on treatment with fluoxetine, 20 mg/day, during detoxification. On initial evaluation, he was depressed, with "racing thoughts," mood swings, and irritability. He was started on dival-

Table 1. Patient Characteristics, Diagnoses, Medications, and Treatment Outcomes[a]

Patient No.[b]	Age, y	Psychiatric Diagnosis (DSM-IV)	Substance-Related Diagnosis (DSM-IV)	Divalproex Dose (maximum)	Other Medications	Treatment Outcome (CGI[c]) and Side Effects	Laboratory Results	Follow-Up After Divalproex Treatment Started	Time Abstinent at Evaluation
1	44	Bipolar I disorder	Alcohol dependence	250 mg bid	Atenolol, 100 mg qd	Improved (2)	Normal; VPA = 32.67	28 d	35 d
2	34	Bipolar II disorder	Alcohol dependence, cannabis abuse	500 mg bid	Fluoxetine, 40 mg qd	Improved (2); slight tremor	Nonsignificant baseline elevations in AST and ALT levels that remained stable after addition of divalproex; VPA = 75.28	56 d	Approximately 2 wk
3	42	Posttraumatic stress disorder, bipolar II disorder	Polysubstance dependence	250 mg bid	Thioridazine, 100 mg bid; clomipramine, 100 mg bid; clonidine, 0.1 mg bid	Improved (2)	Nonsignificant baseline elevations in AST and ALT levels that remained stable after addition of divalproex; VPA = 45.90	23 d	Unknown
4	53	Substance-induced mood disorder	Alcohol dependence	500 mg bid	None	Improved (2)	Normal; VPA = 6.19	14 d	9 mo
5	43	Bipolar I disorder	Alcohol dependence, cocaine dependence	250 mg qam, 500 mg qhs	None	Improved (2); slight tremor	Normal; VPA = 49.50	24 d	92 d
6	28	Bipolar II disorder	Alcohol dependence	500 mg bid	None	NA (0)	NA	None	19 d
7[d]	20	Major depressive disorder	Polysubstance dependence	250 mg qam, 500 mg qhs	Bupropion, 150 mg tid; trazodone, 200 mg qhs; sertraline, 50 mg qd; thioridazine, 75 mg qd + 100 mg tid prn	Improved (2)	Normal; VPA = 58.43	> 45 d	Unknown
8[d]	31	Bipolar II disorder	Polysubstance dependence	750 mg bid	Fluoxetine, 20 mg qd	Improved (2)	Normal; VPA = 21.12	> 1 y	Unknown
9	24	Bipolar I disorder	Polysubstance dependence	250 mg bid	None	None (0)	NA	7 d	29 d
10[d]	25	Bipolar I disorder	Alcohol dependence, cocaine dependence	500 mg qam, 750 mg qhs	Nortriptyline, 75 mg qd	Improved (2)	Nonsignificant baseline elevations in AST and ALT levels that improved over time; VPA = 79.32	Approximately 50 d	50 d
11[d]	36	Bipolar I disorder, panic disorder with agoraphobia	Alcohol dependence, cocaine dependence	1000 mg qam, 750 mg qhs	Buspirone, 10 mg tid; sertraline, 50 mg qd; diphenhydramine, 100 mg qhs	Improved (2)	Normal; VPA = 88.59	> 7 mo	8 mo
12	53	Major depressive disorder	Alcohol dependence	500 mg bid	Trazodone, 200 mg qhs; sertraline, 150 mg qd; buspirone, 10 mg tid	Improved (2)	Normal	7 d	At least 1 wk
13	27	Posttraumatic stress disorder, bipolar II disorder	Alcohol dependence	1000 mg qhs	Fluoxetine, 60 mg qd; trazodone, 300 mg qhs	Improved (2)	Normal; VPA = 32.72	84 d	Unknown
14[d]	35	Bipolar I disorder	Alcohol dependence	500 mg qam, 1000 mg qhs	Perphenazine, 2 mg qhs; paroxetine, 30 mg qd	Improved (2)	NA	18 mo	Unknown
15[d]	55	Bipolar I disorder	Alcohol dependence, cocaine dependence	1000 mg qam, 750 mg qhs	Paroxetine, 40 mg qd; risperidone, 1 mg qhs	Improved (2)	Normal; VPA = 59.18	108 d	108 d
16	30	Attention-deficit/ hyperactivity disorder, bipolar I disorder	Alcohol dependence	250 mg bid	None	NA (0)	Normal	None	45 d

(Continued)

Table 1. Patient Characteristics, Diagnoses, Medications, and Treatment Outcomes (continued)[a]

Patient No.[b]	Age, y	Psychiatric Diagnosis (DSM-IV)	Substance-Related Diagnosis (DSM-IV)	Divalproex Dose (maximum)	Other Medications	Treatment Outcome (CGI[c]) and Side Effects	Laboratory Results	Follow-Up After Divalproex Treatment Started	Time Abstinent at Evaluation
17	26	Panic disorder with agoraphobia, bipolar II disorder	Polysubstance dependence	500 mg bid	Trazodone, 200 mg qhs	Improved (2)	Nonsignificant baseline elevations in AST and ALT levels that improved over time; VPA = 80.12	30 d	14 d
18	42	Bipolar II disorder	Alcohol dependence	750 mg qhs	None	Improved (2); discontinued because of low white blood cell count	White blood cell count low at baseline, further drop after divalproex added; VPA = 65.85	20 d	43 d
19[d]	39	Bipolar I disorder	Alcohol dependence, cannabis abuse	1000 mg bid	Lithium carbonate, 600 mg qam + 300 mg qhs	Improved (2); discontinued because of elevated LFT results	Significant elevations in AST and ALT levels at baseline, continued to rise after addition of divalproex, continued to rise further even after divalproex discontinued; VPA = 93.66	> 2 mo	Unknown
20	33	Bipolar I disorder	Alcohol dependence, cocaine dependence	500 mg qam, 1000 mg qhs	Trazodone, 150 mg qhs; paroxetine, 30 mg qd; buspirone, 10 mg tid; zolpidem, 10 mg qhs	Improved (2)	Normal; VPA = 89.45	60 d	49 d

[a]Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CGI = Clinical Global Impressions scale, LFT = liver function test, VPA = plasma valproate level (μg/mL).
[b]All patients were white men.
[c]CGI scoring as follows: 0 = no follow-up, 1 = much improved, 2 = improved, 3 = slightly improved, 4 = no change.
[d]Patient already taking divalproex at referral.

proex treatment, and the dose was titrated up to 500 mg b.i.d.; fluoxetine was also increased to 40 mg q.d. By his final appointment, almost 2 months later, he was reporting improvement in both depression and lability, saying, "I don't stay upset as long," and "The meds work, they really do." He reported slight tremor; AST and ALT were elevated to clinically insignificant levels at baseline that remained stable during the course of treatment.

Patient 3. A 42-year-old single white man presented with polysubstance dependence, posttraumatic stress disorder, and bipolar disorder, type II. At initial evaluation, he was taking thioridazine, clomipramine, and clonidine, and he was experiencing continued depression and mood lability. He was started with divalproex, 250 mg b.i.d., and after a week reported improvement, saying, "My depression isn't as deep." He reported no side effects. The patient had alcohol-induced liver damage, and baseline elevations in AST and ALT measurements, which remained stable during divalproex treatment.

Patient 12. A 53-year-old divorced white man with alcohol dependence and major depressive disorder presented on treatment with trazodone and sertraline; buspirone was added for anxiety. Four weeks after initial evaluation, because of persistent mood lability despite improvement in anxiety and depression, divalproex, 500 mg b.i.d., was added to his regimen. Within a week, he had resolution of his affective lability and was discharged to a halfway house.

Patient 13. A 27-year-old single white man presented with alcohol dependence, posttraumatic stress disorder, and bipolar disorder, type II. The patient was taking fluoxetine and trazodone. Two weeks after initial evaluation, because of persistent affective lability, divalproex was started, with improvement in mood swings within a week. Divalproex dose was maintained at 1000 mg q.h.s., and the patient was followed for almost 3 months after start of the medication; at discharge, he exhibited no depression or mood swings.

Patient 17. A 26-year-old divorced white man with polysubstance dependence, panic disorder, and bipolar disorder, type II, presented with irritability and mood lability, so divalproex, 500 mg b.i.d., was started. He was also taking trazodone. A week later he reported: "I feel the divalproex has helped me . . . my mood has improved." This improvement persisted until the patient was discharged 4 weeks later. AST and ALT levels, which were slightly elevated at baseline, were normal at discharge.

Patient 18. A 42-year-old divorced white man with alcohol dependence and bipolar disorder, type II, presented with severe mood lability; because he had been treated with divalproex sodium with good results and no side effects in the past, divalproex, 750 mg q.h.s., was started. Two weeks later, the patient reported "The difference with divalproex is dramatic . . . almost instantaneous; in general, I feel much more stable." The patient's baseline

white blood cell count was below normal and dropped slightly after divalproex was started, so the medication was stopped as a precaution, and the patient referred for hematology consultation. Because of discharge to a halfway house, he was lost to follow-up.

Patient 20. A 33-year-old married white man with alcohol dependence, cocaine dependence, and bipolar disorder, type I, presented while taking paroxetine, buspirone, and zolpidem. After a week, because of continued depression and mood swings, he was started on treatment with divalproex, 500 mg b.i.d., which he had taken in the past. At follow-up 3 weeks later, he reported "divalproex has really worked . . . I have not had mood swings for about a week." Divalproex dose was maintained at 500 mg q.a.m. and 1000 mg q.h.s., and the patient was followed for 2 months. At discharge, he continued to be stable.

DISCUSSION

This case series suggests that divalproex sodium is both efficacious and safe to combine with other psychotropic medications in substance-abusing patients with mood disorders who are in post-detoxification, inpatient substance-abuse treatment. The report also suggests that the use of divalproex sodium is safe in this population. These findings are consistent with those of Brady et al.[15] and Sonne and Brady.[17] Fifteen of 17 patients who had laboratory studies conducted after institution of divalproex treatment exhibited unremarkable results. In fact, in 2 cases, AST and ALT levels were slightly elevated at baseline and returned to normal levels after divalproex treatment had been started. In 2 other cases, clinically insignificant baseline elevations remained stable during divalproex treatment; 1 of these patients had been diagnosed with alcohol-induced liver damage.

As has been noted previously, however, the substance-abusing population exhibits higher prevalence of medical disorders than the general population.[18] It has been our experience that some underlying, usually substance-induced medical illnesses, such as liver disease, are frequently undiagnosed in this population, possibly because of the self-care deficits described by Khantzian.[19] This makes it especially imperative that hematology and biochemistry laboratory studies are performed prior to implementing pharmacologic treatment. As noted above, in this cohort, 2 previously undiagnosed patients revealed baseline abnormalities, one with low white blood cell count, the other with elevated liver function test results. Findings such as these might influence the clinician to start with a lower dose of divalproex and titrate more slowly.

Of note, patients received relatively low doses of medication. In some cases, this was because patients did not return for adequate follow-up. Fifteen patients both had follow-up and agreed to have plasma valproate levels measured. Of these, 11 had plasma levels near or within the therapeutic range; all 11 were rated as improved. Interestingly, the other 4 patients were also rated as improved. One explanation is that as these substance-abusing patients achieved further abstinence, their mood improved further. This seems doubtful, since most patients had extensive periods of abstinence before they started medication. Another explanation is that, since this was not a double-blind, placebo-controlled study, both the patients and rater could have been biased when rating improvement. Finally, lower plasma valproate levels might be adequate in this population; in 3 of the 4 patients, levels were greater than 21 μg/mL.

In the 12 patients with known divalproex start date, mean follow-up was 38 days. This is a substantial period of follow-up for dual-diagnosis patients with notoriously poor medication compliance. Of note, 6 other patients were followed; although their divalproex start date was not known exactly, their approximate follow-up periods were 45 days, 50 days, 2 months, 7 months, 12 months, and 18 months. Had these periods been included, the average follow-up period would have been longer.

One strength of this report is the significant period of abstinence prior to commencement of divalproex treatment. In the 10 cases in which a confirmed sobriety date was known, mean period of abstinence was 48 days. In 4 cases, periods were approximately 1 week, 2 weeks, 8 months, and 9 months. Thus, mood difficulty does not appear to have been induced by substance withdrawal.

Incidentally, by self-report, all patients remained abstinent during treatment; some reported decrease in craving. It should be noted that the patients remained in an inpatient treatment setting. Also, since this was an investigation of divalproex for mood disorder in a substance-abusing population, and not for substance abuse symptoms per se, neither measures of craving nor objective measures of substance use (e.g., urine toxicologic analysis) were made. Clearly, more rigorous studies would be needed to determine what role, if any, divalproex plays in either maintenance of sobriety or reduction in craving.

There are obvious limitations to this report. First, it is a case series, not a controlled trial. In addition, most patients were taking more than one medication. Also, diagnoses were made by clinical interview, not structured interview, and changes in status were not based on blinded measures.

The results suggest that divalproex sodium can be used safely, alone and in combination with other psychiatric medications, to effectively treat mood disorders in substance abusers. Double-blind, controlled studies are needed to assess whether divalproex sodium is more effective than other mood stabilizers in this population.

Drug names: atenolol (Tenormin and others), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil and others), clonidine (Catapres and others), diphenhydramine (Benadryl and others) divalproex sodium (Depakote), fluoxetine (Prozac), nortriptyline (Pamelor

and others), paroxetine (Paxil), perphenazine (Trilafon and others), risperidone (Risperdal and others), sertraline (Zoloft), thioridazine (Mellaril and others), trazodone (Desyrel and others), zolpidem (Ambien).

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