

# The Use of Divalproex in the Treatment of Addictive Disorders

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**ABSTRACT** ~ *To date, few medications have shown efficacy in the treatment of addictive disorders. The lack of effective treatments has led to the evaluation of a variety of pharmacotherapies to reduce alcohol or illicit drug use. The anticonvulsant agents are a class of medications that may represent novel treatments for addictive disorders. One of the most studied anticonvulsant agents in the treatment of addictive disorders has been valproate. This article will review the literature regarding the use of valproate in treating alcohol withdrawal symptoms and in reducing the use of alcohol and cocaine. Psychopharmacology Bulletin. 2003;37(Suppl 2): 89-97*

## INTRODUCTION

There has been a growing interest in the use of anticonvulsants as potential treatments for addictive disorders. A variety of anticonvulsants have been studied in the treatment of alcohol withdrawal as well as for their ability to reduce alcohol and cocaine use. In Europe, valproate and carbamazepine have been used successfully to treat alcohol withdrawal for many years. These medications have rarely been used for the treatment of substance use disorders in clinical settings in North America. This is, in part, because most trials of anticonvulsant agents in the treatment of substance use disorders were conducted and published in Europe. The few anticonvulsant trials that were conducted in North America have been published in psychiatric, rather than general medical, literature.<sup>1,2</sup>

Valproate has a long history in the treatment of addictive disorders.<sup>3</sup> This agent is currently available in the United States as valproic acid, sodium valproate, and divalproex sodium which is an enteric-coated compound containing equal proportions of valproic acid and sodium valproate. There are only minor differences in the

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pharmacokinetics of these preparations and the common compound in the plasma is valproic acid. Valproate is approved by the Food and Drug Administration (FDA) for the treatment of migraine headaches, epilepsy, and bipolar affective disorder. Other potential psychiatric uses include panic disorder, posttraumatic stress disorder (PTSD), and behavioral dyscontrol.<sup>4</sup> In this article, the literature regarding the use of valproate in treating addictive disorders will be reviewed.

### ALCOHOL WITHDRAWAL

Up to 71% of individuals presenting for alcohol detoxification will manifest significant symptoms of alcohol withdrawal. Alcohol withdrawal symptoms usually begin 6 to 8 hours after cessation of or reduction in alcohol use. The typical symptoms include tremor, anxiety, nausea, sweating, agitation, headache, and increases in blood pressure and pulse. More serious withdrawal symptoms can include alcohol withdrawal seizures or delirium tremens. The complex symptoms of alcohol withdrawal are the result of multiple neuroadaptive neurotransmitter disturbances in the central nervous system including increased activity of the excitatory glutaminergic system and decreased activity of the inhibitory  $\gamma$ -aminobutyric acidergic system.

In North America, benzodiazepines are the mainstay of treatment of alcohol withdrawal and for two decades have been considered the standard of care as judged by multiple reviews on this topic.<sup>5,6,7,8,9</sup> The use of the benzodiazepines in the treatment of alcohol withdrawal is supported by animal and clinical research and emphasized in several consensus reports issues in the last two decades.<sup>10,11</sup>

While the utility of benzodiazepines in the treatment of uncomplicated alcohol withdrawal is clear, there are several potential advantages to the use of anticonvulsant agents in the treatment of alcohol withdrawal. First, seizures are one of the most serious complications of alcohol withdrawal, and the use of an anticonvulsant medication should decrease the probability of an individual in withdrawal experiencing a seizure. Second, anticonvulsant agents have been shown to block neuronal sensitization or "kindling" in brain cells. There is evidence to support the fact that neuronal sensitization occurs as the result of multiple alcohol detoxifications.<sup>12</sup> Third, anticonvulsants do not have the abuse potential that the benzodiazepines are known to have.<sup>13</sup> This fact has become increasingly important in the last decade as the treatment of alcohol withdrawal has largely moved from inpatient to outpatient settings. While the opportunity to abuse a therapeutic agent is limited in the tight control of an inpatient setting, the abuse potential of an agent is much more clinically relevant when used in an outpatient setting. Fourth, anticonvulsant agents have been found useful in the treatment of affective and anxiety disorders. These disorders

commonly cooccur with alcohol dependence and many of the core symptoms of affective and anxiety disorders, such as depressed mood, sleep disturbance, irritability, and anxiety, are also commonly seen during alcohol withdrawal. Finally, anticonvulsants are less likely to have an acute and additive interaction with alcohol as compared to benzodiazepines if they are consumed together.<sup>14</sup>

The existing literature on the use of valproate in alcohol withdrawal ranges from case reports to large chart reviews and double-blind studies. Bastie<sup>15</sup> reported on the frequency of seizures before and after the use of valproic acid as a standard part of the treatment regime for alcohol withdrawal. Of the 545 alcoholic inpatients who received valproic acid, only one had a seizure compared with a frequency of 2.5% before the introduction of valproic acid. The results are somewhat difficult to interpret because patients also received sedatives and neuroleptics and the dosages of medications used were unclear. Similar problems apply to interpreting the results of Bonfiglio's<sup>16</sup> chart review of 1500 subjects. It was reported that selected symptoms, such as tremor and confusion, were less severe and disappeared more rapidly in valproic acid-treated patients as compared to patients treated with a variety of other medication regimens. Unfortunately, no details of the chart review methodology were provided and there was no statistical analysis of the data reported.

Lambie<sup>17</sup> randomly assigned 48 alcoholics to either valproic acid (1200 mg) therapy or no standing medication, in addition to the conventional prn (as needed) drug therapy (clomethiazole and/or tranquilizers) used in the treatment setting where the study was conducted. Withdrawal symptoms decreased more rapidly and fewer prn medications were required in the valproic acid-treated group. Valproic acid appeared to be well tolerated and there were no seizures reported in the valproic acid group as compared to five subjects experiencing seizures in the control group. However, the data analysis in this study was inadequately described and it is unclear whether severity of alcoholism at baseline was equal in the two groups.

In a double-blind trial comparing valproate, carbamazepine, and placebo in 138 subjects,<sup>18</sup> valproate and carbamazepine were both initiated at 1200 mg per day. There were no measures of alcohol withdrawal symptoms reported, however, alcohol withdrawal seizures occurred in one of 46 valproate subjects, two of 49 carbamazepine subjects, and 3 of 49 placebo subjects. Unfortunately, many of the trial's subjects discontinued treatment due to side effects which the investigators concluded resulted from high initial doses of study medications.

A randomized, open-label comparison of valproate and phenobarbital in 37 subjects experiencing alcohol withdrawal was conducted by Rosenthal and colleagues.<sup>19</sup> While withdrawal symptoms were not significantly

different between the two groups, the phenobarbital group required twice as many prn medications as those treated with valproate. The investigators noted that the valproate was well-tolerated with only one subject experiencing nausea after the initial loading dose of valproate. Unfortunately, there was no indication that the dose of phenobarbital used was equivalent to the valproate dose.

In a small, open-label trial of 11 subjects, Myrick and colleagues<sup>20</sup> compared divalproex to lorazepam. While all subjects in the trial were eligible to receive lorazepam treatment based on an algorithm derived from the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar),<sup>21</sup> one half of the subjects were loaded with divalproex 20 mg/kg and the other subjects did not receive divalproex. There was a rapid decrease in alcohol withdrawal symptoms in the divalproex group as rated by the CIWA-Ar scale as compared to the group who did not receive divalproex. In addition, the divalproex group required less prn lorazepam than the comparison group. Importantly, there was no increase in abnormal liver function tests or decrease in platelets in the divalproex-treated patients.

In a recent placebo-controlled trial,<sup>22</sup> 36 patients were randomized to receive either divalproex or placebo for seven days. Patients could also receive symptom-triggered oxazepam based on the CIWA-Ar. The patients treated with divalproex required significantly less oxazepam and had significantly smaller increases in the CIWA-Ar scores, suggesting better control of alcohol withdrawal symptoms.

### RELAPSE PREVENTION

The successful use of anticonvulsant agents in the treatment of alcohol withdrawal has led to studies exploring their use in relapse prevention. There are several rationales that support these studies. First, substance-dependent individuals may experience a variety of symptoms for weeks to months after cessation of alcohol or drug use. These symptoms include mood instability, anxiety, irritability, and sleep disturbance. This symptom constellation is often referred to as protracted abstinence syndrome and is thought to be related to the many of the same neurotransmitter system alterations seen in acute withdrawal syndromes.<sup>23</sup> Because anticonvulsants are useful in the treatment of acute alcohol withdrawal, these agents are a logical choice for targeting symptoms of protracted abstinence. Anticonvulsants may be effective in reducing the severity of many of the protracted withdrawal symptoms because of their mood-stabilizing and anxiolytic properties. This may prevent self-medication of these symptoms during early recovery by returning to substance use. Second, there are dimensional characteristics such as impulsivity and irritability that underlie many psychiatric disorders, including substance use disorders.<sup>24</sup> There

are a number of case series that support the use of valproate and other anti-convulsant agents in decreasing impulsivity across psychiatric disorders.<sup>4,25-</sup>

<sup>30</sup> In individuals with substance use disorders, impulsivity may be a risk factor for relapse.<sup>31</sup> By decreasing impulsivity, the relapse to substance use may be decreased for some individuals. Finally, many anticonvulsants, including valproate, have GABAergic activity. There is growing interest in the involvement of the GABA system in substance use disorders and in the role of GABAergic agents in relapse prevention.<sup>32-37</sup>

Divalproex has been evaluated in relapse prevention for both alcohol and cocaine use disorders. In a recent double-blind, placebo-controlled trial of divalproex in the prevention of relapse to alcohol use, a smaller percentage of patients on divalproex relapsed to heavy alcohol use.<sup>38</sup> Furthermore, there was a significant decrease in irritability in the divalproex-treated patients. Longo and colleagues<sup>39</sup> reported that in a group initially treated for alcohol withdrawal with divalproex, and then maintained on the medication for six weeks, a greater percentage of patients were completely abstinent as compared to a group of patients whose alcohol withdrawal was treated with a benzodiazepine only.

Myrick and colleagues<sup>40</sup> conducted an eight-week, open-label trial of divalproex in the treatment of cocaine dependence. Baseline rating of craving and frequency of craving decreased from 69% and 61% to 14% and 13%, respectively, by week 8. The percent of positive urine drug screens for cocaine decreased from 64% at baseline to 18% at week 4 and 28% at week 8. Retention in the study was 64% at week 4 and 50% at week 8. The medication and dosing strategy was well tolerated. In addition, Halikas and colleagues<sup>41</sup> found a lower percentage of relapse to cocaine use in 55 subjects treated with open-label divalproex who had valproate serum levels greater than 50 mg/ml than those with less than 50 mg/ml. This literature, while small and preliminary, suggests a role of divalproex in maintaining abstinence in individuals after discontinuing alcohol and drug use.

### COMORBID CONDITIONS

Anticonvulsant agents are effective in treating a variety of psychiatric illnesses, such as bipolar disorder, PTSD, and other anxiety disorders.<sup>4,42-44</sup>

Individuals with these disorders often have concomitant substance use. One approach to the treatment of substance use disorders in individuals with a cooccurring psychiatric disorder is to aggressively treat the underlying psychiatric illness in the hope that use of substances will decrease as the individual no longer needs to self-medicate.

Among all Axis I conditions, bipolar disorder has the highest prevalence of comorbid substance abuse.<sup>45</sup> Epidemiological studies indicate that individuals with bipolar disorder are 6-8 times more likely to have a

substance use disorder when compared to the general population.<sup>45,46</sup> Prevalence rates of alcohol or drug abuse in patients with bipolar disorder have been estimated to range from 21% to 58%.<sup>47</sup> Comorbid substance abuse or dependence can complicate the course of bipolar disorder by prolonging the time to recover from manic or depressive episodes as well as by decreasing time to relapse in patients who have recovered.<sup>48,49</sup> Because valproate is the leading agent in the treatment of uncomplicated bipolar disorder, several studies have examined the utility of the medication in decreasing both the affective symptoms and substance use in persons with comorbid bipolar and substance dependence.

Hammer and Brady<sup>50</sup> found that divalproex loading in two patients with bipolar disorder who were experiencing alcohol withdrawal resulted in a prompt resolution of both affective and withdrawal symptoms. Brady and colleagues,<sup>51</sup> in an open-label study, treated nine subjects with comorbid bipolar disorder and substance use with valproate for a mean of 16 weeks. Significant decreases in affective symptoms and substance use were noted. Valproate was well-tolerated and no significant liver enzyme elevation was found. A retrospective chart review by Hertzman<sup>52</sup> found a reduction in substance use in individuals with comorbid substance use and mood disorders who were treated with divalproex.

A recent double-blind study evaluated the efficacy of valproate in decreasing alcohol use and stabilizing affective symptoms in 52 actively drinking bipolar alcohol-dependent individuals.<sup>53</sup> Subjects were randomized to valproate plus treatment as usual or placebo plus treatment as usual. Treatment as usual included lithium and psychosocial treatment. Over the 24-week treatment period, subjects in both groups had improvement in affective symptoms. However, the valproate-treated subjects had a lower proportion of heavy drinking days than the placebo-treated subjects. While not reaching statistical significance, valproate-treated subjects also had a lower proportion of any drinking days. Weiss and colleagues<sup>54</sup> found better compliance and tolerability with valproate treatment compared to lithium treatment in 44 individuals with comorbid bipolar disorder and substance use.

#### **SAFETY CONSIDERATIONS**

There are several factors that need particular consideration when using valproate in individuals with addictive disorders. The use of valproate is commonly associated with a benign decrease in platelet count, but there have been rare cases of thrombocytopenia reported.<sup>55-57</sup> Chronic alcohol use is associated with general suppression of bone marrow function. With this in mind, careful monitoring of platelet function when initiating valproate treatment in alcohol-dependent individuals, and other individuals who may have compromised hematopoietic function, is recommended.

There have also been some reports of hepatotoxicity with valproate treatment, although nearly all of these cases involve the use of valproate in children for the treatment of seizure disorder.<sup>58</sup> Because individuals with substance use disorders may have compromised liver function for a number of reasons, monitoring of liver enzymes during valproate initiation is also recommended. However, Sonne and Brady<sup>59</sup> reported on twenty patients with comorbid bipolar disorder and alcoholism who were treated with valproate. The patients had no evidence of preexisting liver disease and were followed for an average of five months. There was no significant increase in liver enzymes during the study period even though some individuals continued to use alcohol throughout the study. There was a decrease in platelet count observed, but this decrease did not reach clinical significance for any patients studied.

A recent report suggests that valproate can be safely used in patients with hepatitis C virus.<sup>60</sup> This is especially important given the high incidence of hepatitis C virus in individuals with substance use disorders. While lacking definitive data, a general rule would be to not initiate use of valproate in an individual who has liver enzyme elevation of greater than 3 times normal or a platelet count below 100.

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### **CONCLUSIONS**

There is considerable information regarding the use of valproate in the treatment of addictive disorders. Many of these studies report the effective use of valproate in the treatment of alcohol withdrawal. Unfortunately, many of the studies are open label or chart review in nature. Large, randomized, double-blind trials comparing valproate to a benzodiazepine are needed. More recent studies have investigated the use of valproate in reducing alcohol and cocaine use and in the treatment of individuals with co-occurring substance use disorders and psychiatric disorders. While the results thus far are encouraging, large randomized, double-blind trials are needed to provide further evidence of valproate's effectiveness. ❁

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**DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS**

Please note that this review article contains discussions of unlabeled uses of FDA-approved pharmaceutical products. Please refer to the official prescribing information for approved indications, contraindications, and warnings.

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